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QUINAZOLINE BASED PROTEIN KINASE INHIBITORS

Abstract:

1019 Abstract of WO2005097134

Hydroxy containing quinazoline based derivatives have enhanced and unexpected drug properties as inhibitors of protein kinases and are useful in treating disorders related to abnormal protein kinase activities such as cancer. Data supplied from the esp@cenet database - Worldwide

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(54) Title: QUINAZOLINE BASED PROTEIN KINASE INHIBITORS

(57) Abstract: Hydroxy containing quinazoline based derivatives have enhanced and unexpected drug properties as inhibitors of protein kinases and are useful in treating disorders related to abnormal protein kinase activities such as cancer.

WO 2005/097134 A2

QUINAZOLINE BASED PROTEIN KINASE INHIBITORS

Description

Field of Invention

This invention relates to protein kinase inhibitors and to their use in treating disorders related to abnormal protein kinase activities such as cancer and inflammation. More particularly, the invention relates to quinazoline based protein kinase compounds and their pharmaceutically acceptable salts employable as protein kinase inhibitors.

Background

Protein kinases are enzymes that catalyze the phosphorylation of hydroxyl groups of tyrosine, serine, and threonine residues of proteins. Many aspects of cell life (for example, cell growth, differentiation, proliferation, cell cycle and survival) depend on protein kinase activities. Furthermore, abnormal protein kinase activity has been related to a host of disorders such as cancer and inflammation. Therefore, there is a great deal of effort directed to identifying ways to modulate protein kinase activities. In particular, many attempts have been made to identify small molecules which act as protein kinase inhibitors.

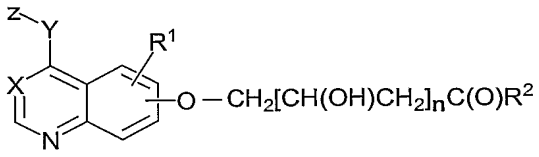
Quinazoline and quinoline based derivatives having activity as protein kinase inhibitors have been disclosed in International Patent Applications WO 0132651, WO 0174360, WO 0212226, WO 0340108, WO 0340109, WO 0216361, WO 0216351, and WO 0236587. What is needed is a class of modified quinazoline based derivatives having both activity as protein kinase inhibitors and enhanced drug properties.

Summary:

The invention is directed to hydroxy containing quinazoline derivatives and to their use as inhibitors of protein kinases. It is disclosed herein that

hydroxy containing quinazoline derivatives have enhanced and unexpected drug properties that advantageously distinguish this class of compounds over known quinazoline derivatives having protein kinase inhibition activity. It is also disclosed herein that hydroxy containing quinazoline derivatives are useful in treating disorders related to abnormal protein kinase activities such as cancer.

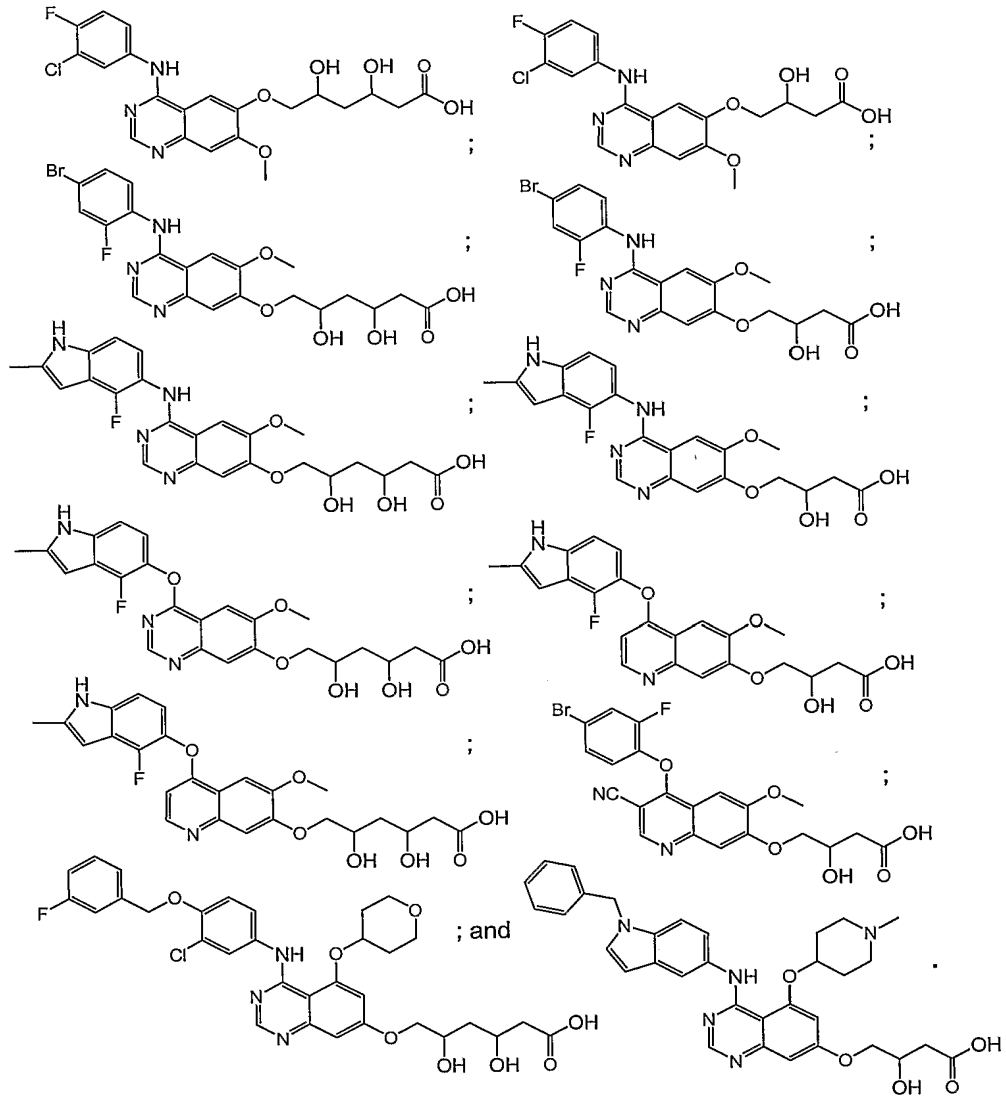
One aspect of the invention is directed to a compound represented by Formula (**I**):



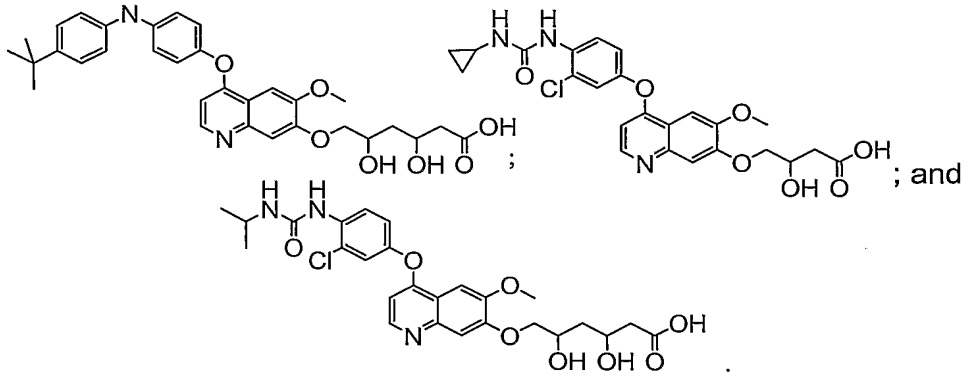
(Formula I)

In Formula I, X is a triradical selected from the group consisting of N and C(R^3); Y is a diradical selected from the group consisting of N(R^4) and O; Z is a radical selected from the group consisting of optionally substituted phenyl, pyridine, indole, indazole, naphthalene, benzofuran, and benzothiophene; R^1 is a radical selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) alkoxy, (C3-C8) cycloalkoxy, and (C5-C8) heterocycloalkoxy; R^2 is a radical selected from the group consisting of hydroxyl, (C1-C6) alkoxy, (C5-C8) cycloalkoxy, and -NR^5R^6; **n** is 1 or 2; R^3 is a radical selected from the group consisting of hydrogen and nitrile; R^4 is a radical selected from the group consisting of hydrogen and (C1-C6) alkyl; R^5 and R^6 are independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C1-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C1-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphoric acid, (C1-C6) alkyl sulfuric acid, (C1-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C10) aryl, (C5-C9) heteroaryl, (C3-C8) cycloalkyl carboxylic acid; or R^5 and R^6 together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids; or NR^5R^6 may form a cyclic ring containing 0-3 additional heteroatoms selected from N, O, or S; or, a pharmaceutically acceptable salt, its tautomer, a pharmaceutically acceptable salt of its tautomer, or a prodrug thereof.

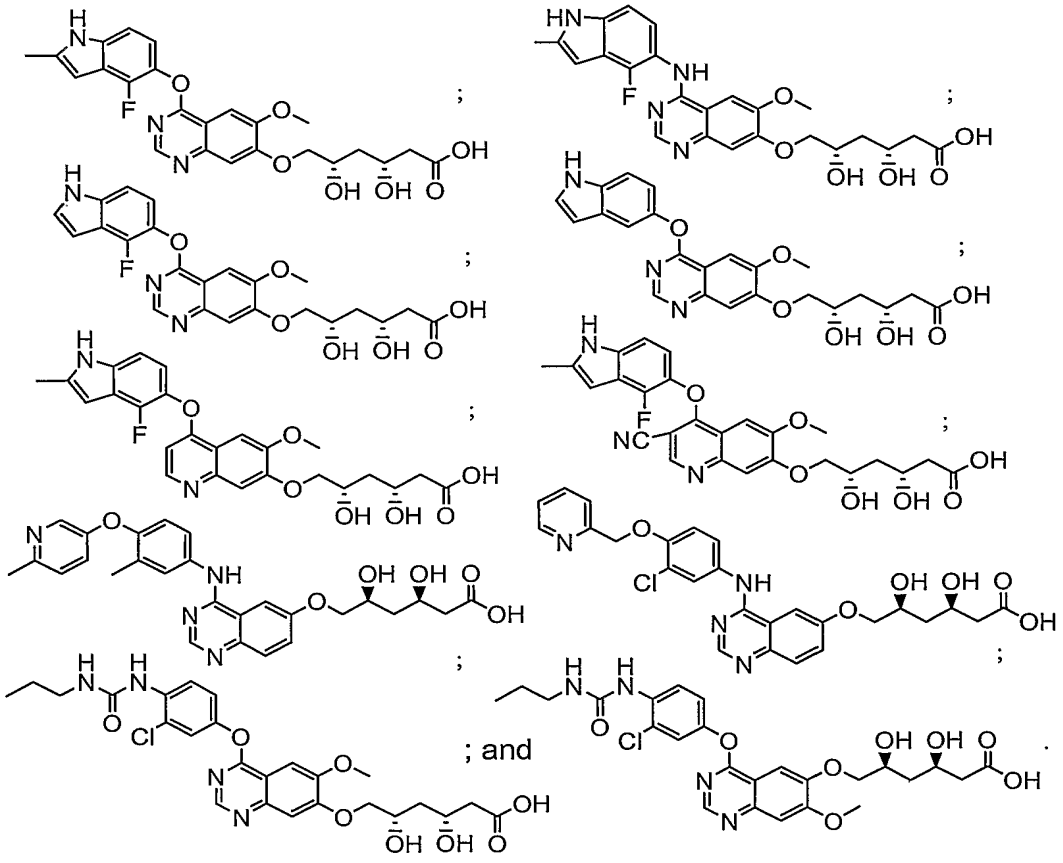
In a first preferred subgenus of this first aspect of the invention, R^2 is a radical selected from the group consisting of hydroxyl, (C1-C6) alkoxy, and (C5-C8) cycloalkoxy. Preferred embodiments of this first subgenus compounds represented by the following structures:



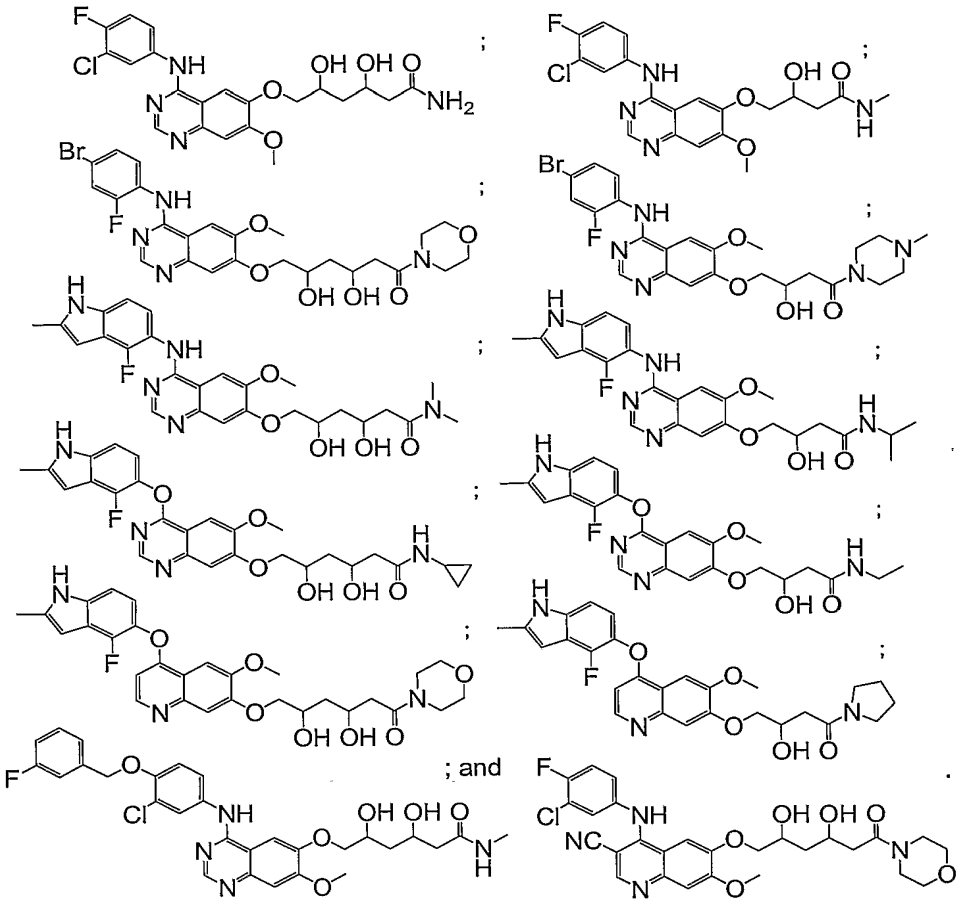
Further embodiments of the first subgenus of the first aspect of the invention include compounds represented by the following structures:



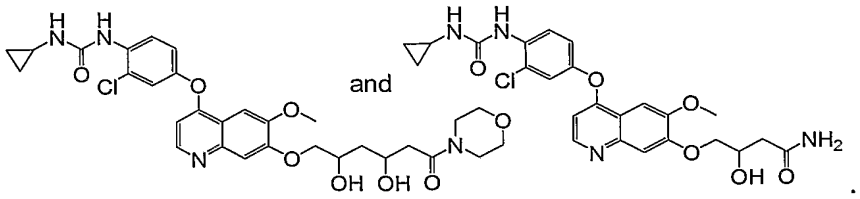
Further embodiments of the first subgenus of the first aspect of the invention include compounds represented by the following structures:



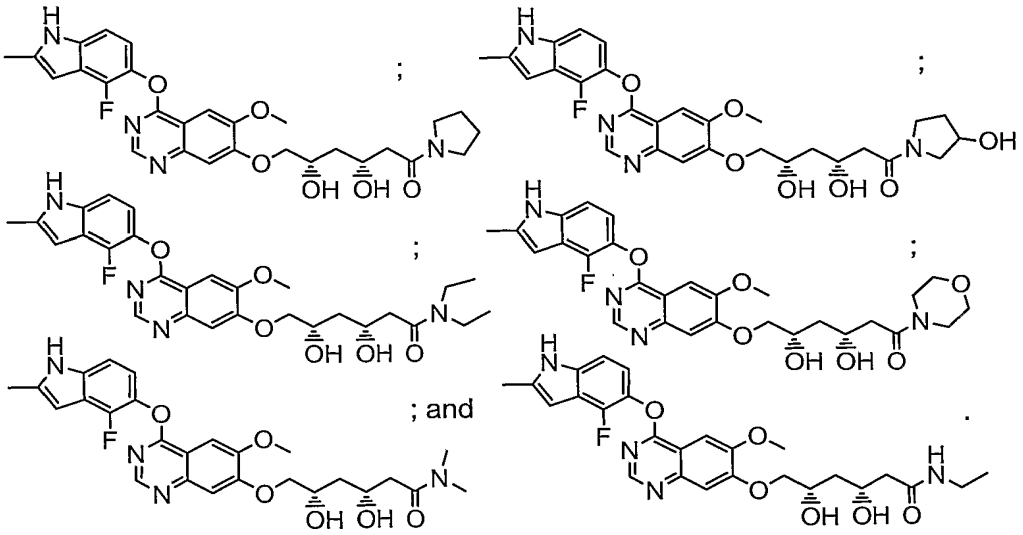
In a second preferred subgenus of the first aspect of the invention represented by Formula I, R^2 is $-NR^5R^6$. Embodiments of the second subgenus of the first aspect of the invention include compounds represented by the following structures:



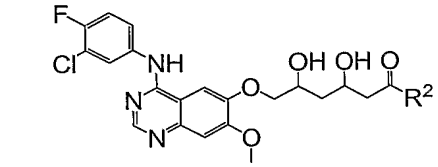
Further embodiments of the second subgenus of the first aspect of the invention include compounds represented by the following structures:



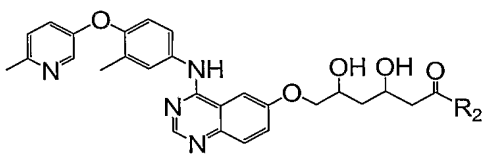
Further embodiments of the second subgenus of the first aspect of the invention include compounds represented by the following structures:



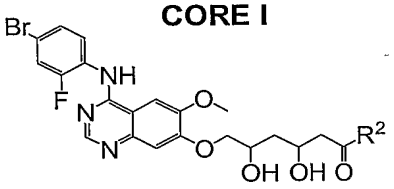
Further embodiments of the second subgenus of the first aspect of the invention include compounds represented by the following structures:



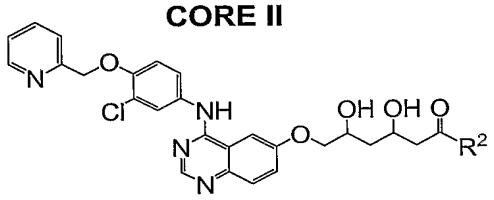
CORE I



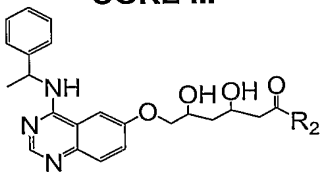
CORE II



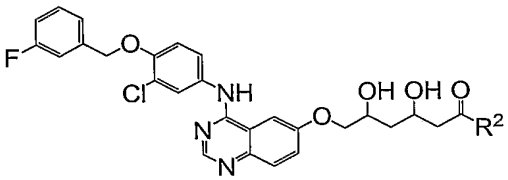
CORE III



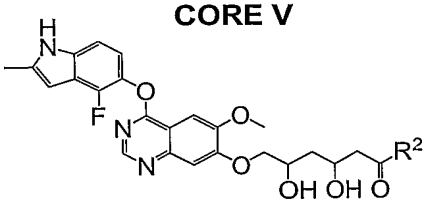
CORE IV



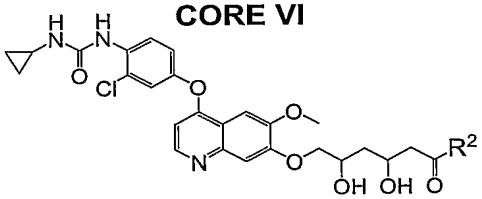
CORE V



CORE VI



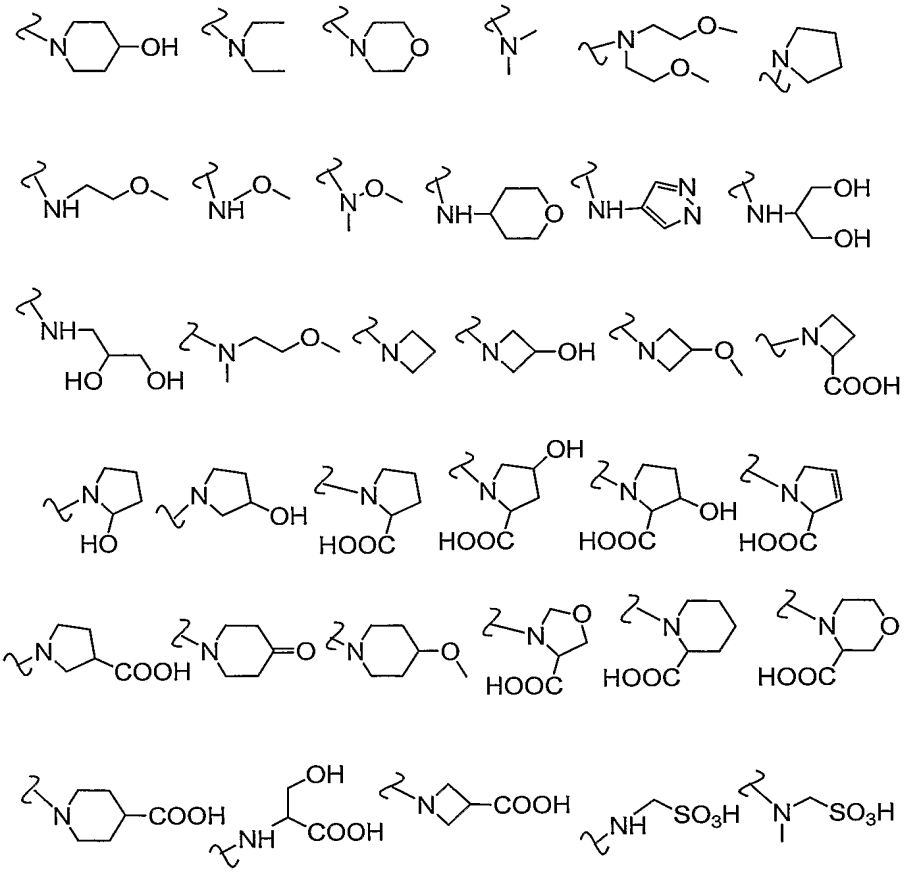
CORE VII



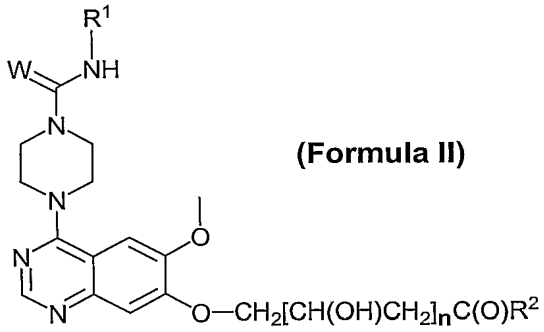
CORE VIII

5

In each of the CORE structures (I-VIII), R^2 is selected from the group consisting of radical represented by the following structures:



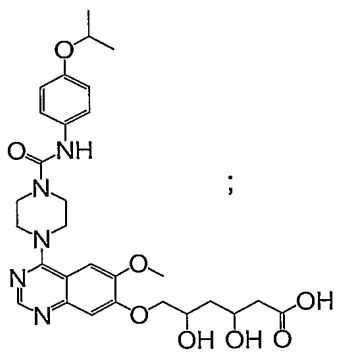
A second aspect of the invention is directed to a compound of formula (**II**):



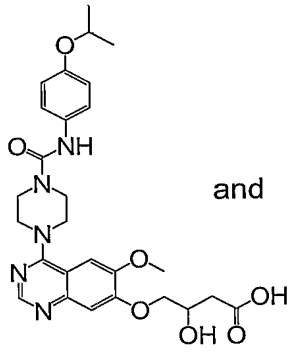
(Formula II)

In Formula II, W is a diradical selected from the group consisting of O and S; R^1 is a radical selected from the group consisting of optionally substituted phenyl, benzyl, heteroaryl, and heteroarylalkyl; R^2 is a radical selected from the group consisting of hydroxyl, (C1-C6) alkoxy, (C3-C8) cycloalkoxy, and NR^3R^4; **n** is 1 or 2; R^3 and R^4 are independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C1-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C1-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphoric acid, (C1-C6) alkyl sulfonic acid, (C1-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C10) aryl, (C5-C9) heteroaryl, (C3-C8) cycloalkyl carboxylic acid; or R^3 and R^4 together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids; or NR^3R^4 may form a cyclic ring containing 0-3 additional heteroatoms selected from N, O, or S; or, a pharmaceutically acceptable salt, its tautomer, a pharmaceutically acceptable salt of its tautomer, or a prodrug thereof.

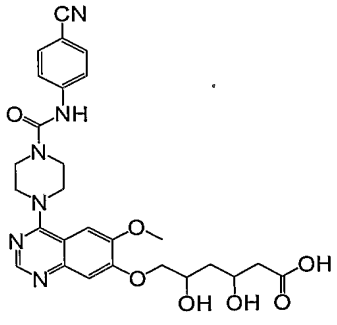
In a first preferred subgenus of this second aspect of the invention represented by Formula II, R^2 is a radical selected from the group consisting of hydroxyl, (C1-C6) alkoxy, and (C5-C8) cycloalkoxy. Embodiments of the first subgenus of the second aspect of the invention include compounds represented by the following structures:



;



and



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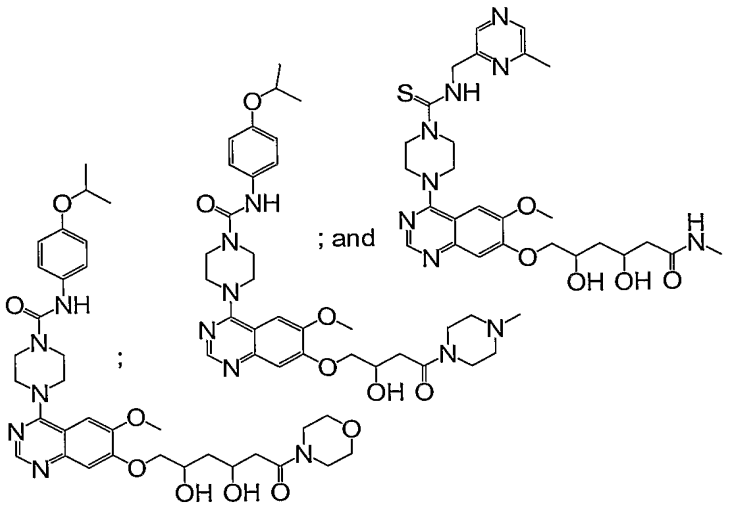
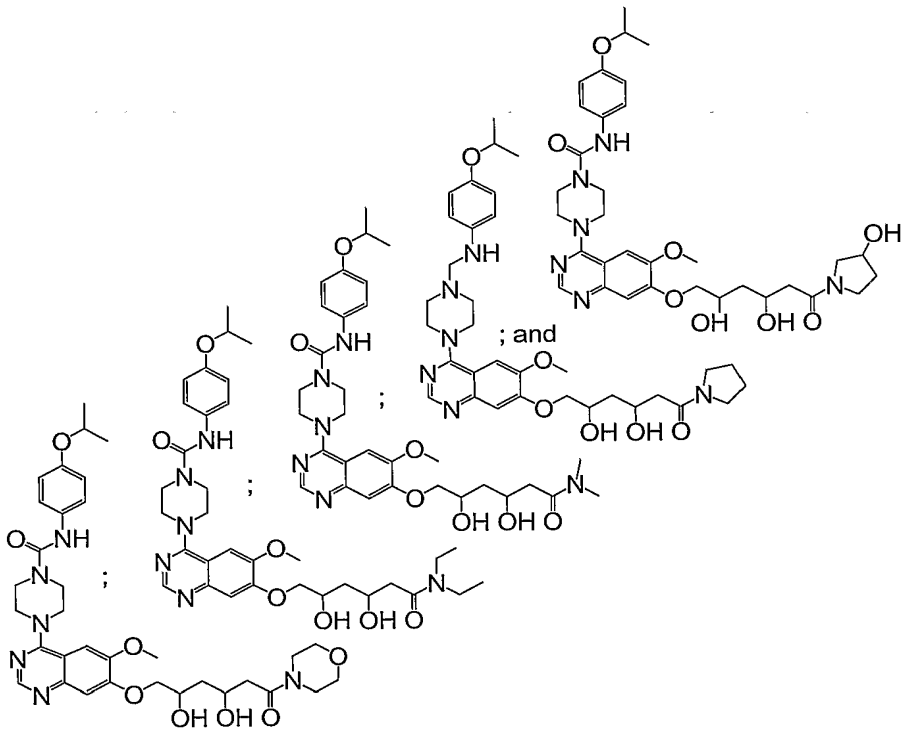
In a second preferred subgenus of this second aspect of the invention represented by Formula II, R^2 is $-NR^5R^6$. Preferred embodiments of the second

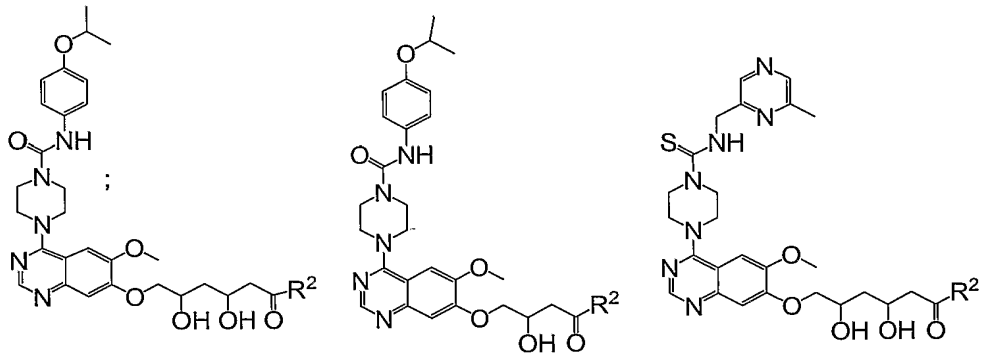
subgenus of the second aspect of the invention include compounds represented by the following structures:



Further embodiments of the second subgenus of the second aspect of the invention include compounds represented by the following structures:

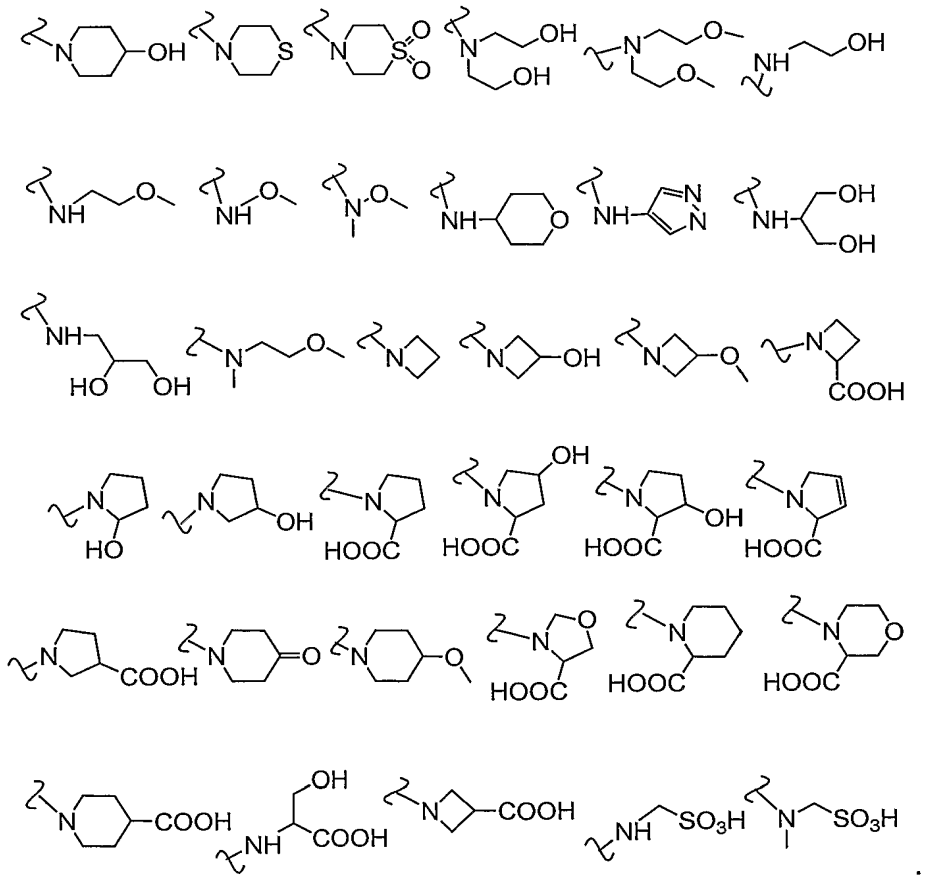


Further embodiments of the second subgenus of the second aspect of the invention include compounds represented by the following structures:



CORE I CORE II CORE III

wherein: R^2 is selected from the group consisting of radical represented by the following structures:

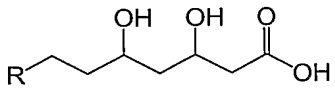


Provisos may apply to any of the above inventive aspects, subgenera, or embodiments wherein any one or more of the other above described embodiments or species may be excluded from its corresponding inventive aspect, subgenus, or embodiments.

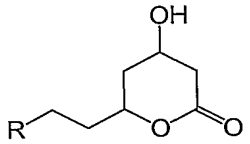
A third aspect of the invention is directed to a method for the modulation of the catalytic activity of a protein kinase with a compound or salt of any one of Formula I or Formula II. In a preferred embodiment of the third aspect of the invention, the protein kinase is a VEGF receptor, FGF receptor, EGF receptor, or PDGF receptor.

This invention discloses that certain hydroxy compounds may have interesting and unexpected properties that advantageously distinguish them from known compounds. They are therefore useful in treating disorders related to abnormal protein kinase activities such as cancer.

It should be understood that a compound of Formula (**I**) or (**II**) where R^2 is OH may exist in its open-acid form or its cyclic-lactone form or the two forms may co-exist in solution or *in vivo* as illustrated below:



Open-acid form



Cyclic-lactone form

Furthermore, all compounds of Formula (**I**) or (**II**) have at least one asymmetric center and the stereochemistry at the asymmetric center(s) is (are) either *RS*, *R*, or *S*.

Brief Description of Drawings:

Figure 1 illustrates a scheme showing the synthesis of the 6-(omega alkanoic acid) quinazolines from 6,7-dimethoxy-3,4-dihydroquinazolin-4-one.

Figure 2 illustrates is a scheme showing the synthesis of **2-Na**, which is the 7-(omega alkanoic acid) quinazoline derivative, from 7-benzyloxy-4-chloro-6-methoxyquinazoline.

Figure 3A illustrates a table of preferred compounds of the invention. All of the compounds shown have at least one asymmetric center and the stereochemistry at any given asymmetric center is *RS*, *R*, or *S*.

Figure 3B illustrates a table of preferred compounds of the invention. All of the compounds shown have at least one asymmetric center and the stereochemistry at any given asymmetric center is *RS*, *R*, or *S*.

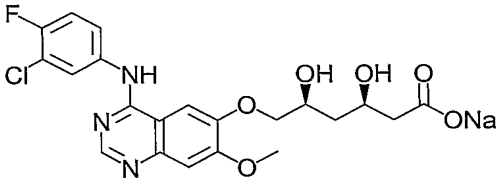
Figure 3C illustrates a table of preferred compounds of the invention. All of the compounds shown have at least one asymmetric center and the stereochemistry at any given asymmetric center is *RS*, *R*, or *S*.

Figure 4 illustrates a table of preferred compounds of the invention. All of the compounds shown have at least one asymmetric center and the stereochemistry at any given asymmetric center is *RS*, *R*, or *S*.

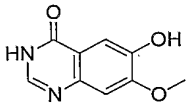
Detailed Description:

The compounds of this invention can be synthesized by following the published general procedures. But the following intermediates are specific to compounds of this invention and may be used in place of their respective counterparts in the published general procedures: ethyl (3*R*,5*S*)-6-hydroxy-3,5-O-isopropylidene-3,5-dihydroxyhexanoate, ethyl (*R*)-4-chloro-3-hydroxybutyrate, and ethyl (*S*)-4-chloro-3-hydroxybutyrate. These intermediates may be purchased from commercial sources (e.g. Takasago International Corp., Rockleigh, New Jersey). This change from the published general procedures can be understood and carried out by those skilled in the art. The amides of Tables 1-2 can be readily synthesized from their corresponding acids. Thus, the compounds of the present invention can be synthesized by those skilled in the art.

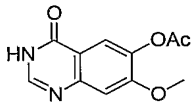
Example 1: (3*R*,5*S*)-6-[4-(3-Chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]oxy-3,5-dihydroxy-hexanoic acid sodium salt.



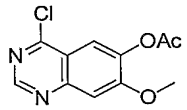
The procedure for the synthesis of the title compound is depicted in Figure 1.



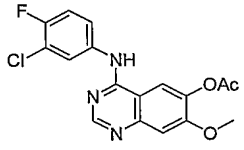
1-2: 6-Hydroxy-7-methoxy-3,4-dihydroquinazolin-4-one was obtained according to WO96/33980 in 93% yield. ^{1}H NMR (DMSO-d_6, ppm): δ 7.92 (s, 1H), 7.39 (s, 1H), 7.09 (s, 1H), 3.89 (s, 3H). ^{13}C NMR (DMSO-d_6, ppm): δ 160.0, 153.8, 152.3, 146.4, 143.7, 115.9, 108.6, 108.1, 55.9.



1-3: 6-Acetoxy-7-methoxy-3,4-dihydroquinazolin-4-one was obtained according to WO96/33980 in 82% yield. The crude product was used for the next step without purification.

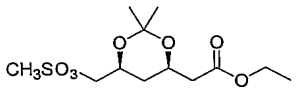


1-4: 4-Chloro-6-acetoxy-7-methoxyquinazoline hydrochloride was obtained according to WO96/33980 and used for the next step without purification.

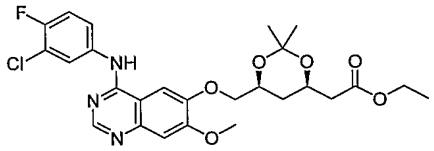


1-5: 4-(3'-Chloro-4'-fluoroanilino)-6-acetoxy-7-methoxyquinazoline hydrochloride was obtained according to WO96/33980 in 82% yield from **1-4**. The crude material was used for the next step without purification.

1-6: 4-(3'-Chloro-4'-fluoroanilino)-6-hydroxy-7-methoxyquinazoline was obtained according to WO96/33980 in 90% isolated yield. ^{1}H NMR (DMSO-d_6, ppm): δ 9.64 (br s, 1H), 9.38 (br s, 1H), 8.37 (s, 1H), 8.10 (dd, 1H, *J* = 8.1, 2.7 Hz), 7.72 (m, 1H), 7.66 (s, 1H), 7.30 (t, *J* = 9.0 Hz, 1H), 7.11 (s, 1H), 3.87 (s, 3H). ^{13}C NMR (DMSO-d_6, ppm): δ 155.7, 153.8, 152.7 (d, *J* = 241.6 Hz), 151.8, 146.6, 146.0, 137.0, 122.6, 121.6 (d, *J* = 6.7 Hz), 118.6 (d, *J* = 18.0 Hz), 116.3 (d, *J* = 21.6 Hz), 109.5, 107.1, 105.2, 55.9.

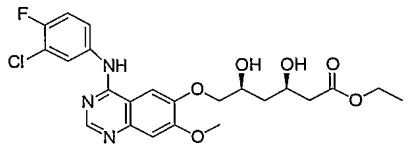


1b: (4*R*,6*S*)-(6-Methanesulfonyloxymethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid ethyl ester was obtained according to a known method (H. Jendralla, E. Granzer, B. Von Kerekjarto, R. Krause, U. Schacht, E. Baader, W. Bartmann, G. Beck, A. Bergmann, et al.; Synthesis and biological activity of new HMG-CoA reductase inhibitors. 3. Lactones of 6-phenoxy-3,5-dihydroxyhexanoic acids. *J. Med. Chem.* **1991**, *34*, 2962 – 2983) in 91% isolated yield. ^{1}H NMR ($CDCl_3$, ppm): δ 4.38-4.34 (m, 1H), 4.23-4.12 (m, 1H), 3.06 (s, 3H), 2.60-2.36 (m, 2H), 1.62 (d, 1H, *J* = 12.6 Hz), 1.47 (s, 3H), 1.38 (s, 3H), 1.32 (m, 1H), 1.26 (t, 3H, *J* = 6.9Hz). ^{13}C NMR (DMSO-d_6, ppm): δ 170.6, 99.3, 72.3, 67.3, 65.6, 60.8, 41.4, 37.9, 31.9, 30.0, 19.9, 14.5.

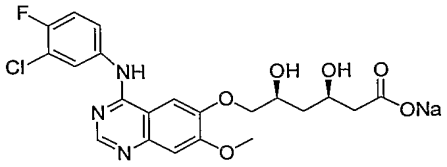


1-7: (4*R*,6*S*)-{6-([4-(3-Chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]oxymethyl)-2,2-dimethyl-[1,3]dioxan-4-yl}-acetic acid ethyl ester was obtained in analogy to the publication (Jendralla, H.; et al. *J. Med. Chem.* **1991**, *34*, 2926-2983). A mixture of **1-6** (0.32 g, 1.0 mmol), **1b** (0.33 g, 1.0 mmol), K_2CO_3 (0.38 g, 2.75 mmol), 18-crown-6 (1 mg), and DMAc (5 mL) was heated at 91 °C for 7 h. Another 0.2 g (0.6 mmol) of **1b** was added. Heating at 91 °C was continued for 17 h and the mixture was cooled to room temperature. Water (20 mL) and saturated sodium bicarbonate solution (20 mL) were added. The obtained solution was extracted with MTBE (60 mL × 3), the combined organic layers were washed with saturated sodium bicarbonate solution (50 mL) and saturated

sodium chloride solution (50 mL), dried over $MgSO_4$, and concentrated to give the crude product (0.50 g) as a viscous syrup. The crude material was subjected to chromatography on silica eluting with heptane/ethyl acetate (3:1, 2:1 and 1:1) to give pure **1-7** (0.28 g, 50%) as a pale yellow solid. Mp 135-136 °C. ^{1}H NMR (300 MHZ, CD_3OD, ppm): δ 8.27 (s, 1H), 7.95 (dd, 1H, *J* = 6.9, 2.7 Hz), 7.58 (m, 1H), 7.20 (s, 1H), 7.14 (t, *J* = 9.0 Hz, 1H), 6.77 (s, 1H), 4.40 (m, 2H), 4.20-3.81 (m, 4H), 3.78 (s, 3H), 2.49 (d, 2H, *J* = 6.3 Hz), 1.73 (d, 1H, *J* = 12.9 Hz), 1.52 (s, 3H), 1.36 (s, 3H), 1.26 (t, 3H, *J* = 6.9 Hz), 1.25 (m, 1H). ^{13}C NMR (75 MHz, CD_3OD, ppm): δ 172.2, 157.4, 155.9, 155.3 (d, *J* = 244.0 Hz), 153.3, 149.5, 147.0, 137.2, 125.0, 123.0 (d, *J* = 6.7 Hz), 120.9 (d, *J* = 18.0 Hz), 117.0 (d, *J* = 21.6 Hz), 109.7, 106.8, 102.7, 100.3, 73.2, 69.0, 67.0, 61.6, 56.4, 42.3, 30.3, 20.1, 14.6.

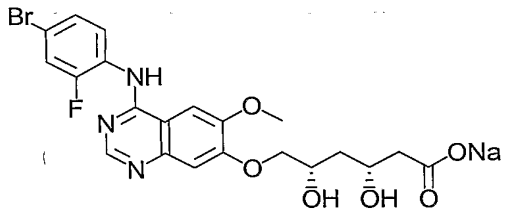


1-8: (3*R*,5*S*)-6-{[4-(3-Chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]oxy}-3,5-dihydroxyhexanoic acid ethyl ester was obtained in analogy to previous publication (Jendralla, JMC, **1991**). The material was used for next step without purification. A suspension of **1-7** (0.28 g, 0.51 mmol) and aqueous HCl solution (2 N, 0.56 mL) in ethanol (6 mL) and THF (3 mL) was stirred at 20 °C for 24 h. Saturated aqueous Na_2CO_3 solution (ca. 4 mL) was added to adjust to pH 9. The solvent was evaporated to give a solid residue to which water (10 mL) was added. The solution was lightly extracted with EtOAc (40 mL × 2). The combined organic layers were dried over $MgSO_4$, concentrated to give the product (0.12 g, 46%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.40 (s, 1H), 7.75 (dd, 1H, *J* = 6.6, 2.4 Hz), 7.44 (m, 1H), 7.18 (s, 1H), 6.95 (t, *J* = 9.0 Hz, 1 H), 6.84 (s, 1H), 4.30 (br s, 2H), 4.08-3.81 (m, 4H), 3.63 (s, 3H), 2.49 (d, 2H, *J* = 5.7 Hz), 1.69 (br s, 2H), 1.20-1.11 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 172.3, 156.4, 154.8, 154.5 (d, *J* = 246.4 Hz), 152.9, 148.2, 146.1, 135.5, 124.2, 122.0 (d, *J* = 6.5 Hz), 120.6 (d, *J* = 18.6 Hz), 116.3 (d, *J* = 21.6 Hz), 108.7, 106.5, 102.2, 73.1, 69.3, 67.9, 61.1, 56.1, 42.1, 39.2, 14.4.



1-Na: 6-{[4-(3-Chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]oxy}-3,5-dihydroxyhexanoic acid. A solution of **1-8** (0.20 g, 0.39 mmol) and aqueous NaOH solution (0.51 N, 0.77 mL, 0.39 mmol) in methanol (6 mL) was stirred at 20 °C for 24 h. The solvents were evaporated. The residue was dissolved in water (20 mL), extracted with MTBE (30 mL), and lyophilized to give **1-8** as a pale orange solid (210 mg, 99% yield). Mp 225 °C (decomposition). ^{1}H NMR (300 MHz, CD_3OD, ppm): δ 8.39 (s, 1H), 8.01 (dd, 1H, *J* = 6.6, 2.1 Hz), 7.62 (m, 2H), 7.19 (t, *J* = 9.0 Hz, 1H), 7.05 (s, 1H), 4.32-4.07 (m, 4H), 3.96 (s, 3H), 2.42 (m, 2H), 1.86 (m, 2H). ^{13}C NMR ($CDCl_3$, ppm): δ 180.1, 157.9, 156.2, 155.6 (d, *J* = 267.3 Hz), 153.6, 150.0, 147.3, 137.4, 125.3, 123.4, 121.0 (d, *J* = 18.0 Hz), 117.1 (d, *J* = 21.6 Hz), 110.3, 107.0, 103.4, 74.4, 69.0, 68.5, 56.6, 45.7, 41.4.

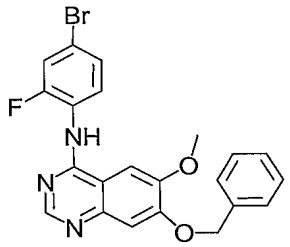
Example 2: (3*R*,5*S*)-6-[{4-(4-Bromo-2-fluorophenylamino)-6-methoxyquinazolin-7-yl}oxy]-3,5-dihydroxyhexanoic acid, sodium salt.



The synthesis of the title compound, outlined in Figure 2, was accomplished in six steps from compound **2-2** (purchased from J.W. Pharmlab). Intermediates **2-3** and **2-4** were prepared by the method of Hennequin *et al.* (Hennequin, L.F.; Thomas, A.P.; Johnstone, C.; Stokes, E.S.E.; Ple, P.A.; Lohmann, J.M.; Ogilvie, D.J.; Dukes, M.; Wedge, S.R.; Curwen, J.O.; Kendrew, J.; Brempt, L. *J. Med. Chem.* **1999**, *42*, 5369-5389). Intermediate **2-4** was then coupled with the mesylate of **EHA**, which was prepared from **EHA** (provided by Takasago). Both the coupling and the preparation of the mesylate were conducted by the methods of Jendralla *et al.* Once the coupling was complete, **2-5** was treated with dilute hydrochloric acid to remove the acetonide protective group. The ester

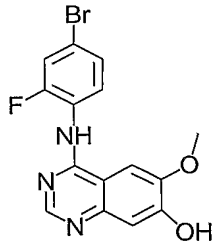
2-7 was then converted to the salt **2-Na** by treatment with one equivalent of sodium hydroxide.

2-3: (7-Benzyloxy-6-methoxyquinazolin-4-yl)-(4-bromo-2-fluorophenyl)-amine



A mixture of **2-2** (7-benzyloxy-4-chloro-6-methoxyquinazoline, obtained from J. W. Pharmlab, 2.05 g, 6.81 mmol) and 4-bromo-2-fluoroaniline (3.04 g, 15.9 mmol) was heated to reflux in isopropyl alcohol (80 mL) for 24 hours. After cooling to room temperature, the mixture was made basic with sodium bicarbonate (1.0 g) in DIUF water (10 mL). The mixture was concentrated under reduced pressure and dried under high vacuum before purification by flash column chromatography on silica gel (80 g), eluting with 1-10% methanol in dichloromethane. The procedure produced **2-3** as a light yellow solid (1.37 g, 45% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.48 (s, 1H), 8.33 (s, 1H), 7.80 (s, 1H), 7.56-7.33 (m, 8H), 7.26 (s, 1H), 5.26 (s, 2H), 3.94 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.69, 156.46 (d, J = 249.6 Hz), 153.10, 152.77, 148.92, 146.64, 136.14, 129.42, 128.37, 127.89, 127.39, 126.23 (d, J = 12.0 Hz), 119.21 (d, J = 23.2 Hz), 117.45 (d, J = 9.0 Hz), 108.65, 108.22, 101.91, 69.92, 56.12.

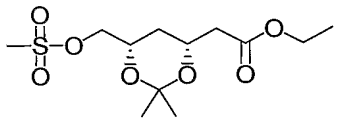
2-4: 4-(4-Bromo-2-fluorophenylamino)-6-methoxyquinazolin-7-ol



Intermediate **2-3** (1.30 g, 2.86 mmol) was dissolved in trifluoroacetic acid (15 mL) and the solution was heated to reflux for 1.5 hours. The solution was cooled

to room temperature and concentrated under reduced pressure. Methanol (20 mL) was added to the remaining brown solid and the pH was adjusted to 11 with concentrated ammonium hydroxide. The mixture was concentrated under reduced pressure and dried under high vacuum before purification by flash column chromatography on silica gel (20 g), eluting with 5-20% methanol in dichloromethane. The experiment generated **2-4** (1.03 g, 99% yield) as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.5 (br s, 1H), 9.53 (br s, 1H), 8.34 (s, 1H), 7.81 (s, 1H), 7.63 (d, 1H, *J* = 9.6 Hz), 7.54 (dd, 1H, *J* = 8.4, 7.8 Hz), 7.44(d, 1H, *J* = 8.4 Hz), 7.12 (s, 1H), 3.95 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.77, 156.49, 152.92, 152.62, 148.62, 146.74, 129.40, 127.39, 126.46 (d, *J* = 12 Hz), 119.23 (d, *J* = 23.2 Hz), 117.4 (d, *J* = 8.3 Hz), 109.96, 108.08, 102.23, 56.09.

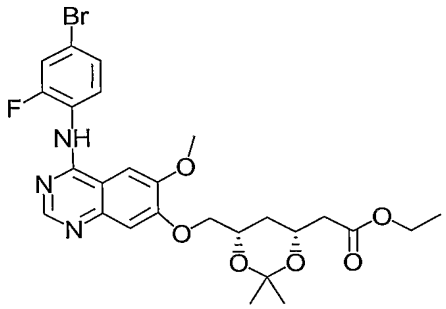
EHA-Ms: ((4*R*,6*S*)-6-Methanesulfonyloxymethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid ethyl ester



Under argon atmosphere, EHA ((4*R*,6*S*)-6-hydroxymethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid ethyl ester 0.5 g, 2.15 mmol, provided by Takasago) was dissolved in anhydrous dichloromethane (3.0 mL) with pyridine (1.0 mL). The flask was cooled in an ice-water bath and methanesulfonyl chloride (0.5 g, 4.36 mmol) in dichloromethane (1.0 mL) was added dropwise over 5 minutes. The solution was stirred for 1 hour at 5 °C. Toluene (20 mL) was added and the solution was concentrated under reduced pressure. An additional portion of toluene (20 mL) was added and the solution was extracted with saturated sodium bicarbonate solution (20 mL) and DIUF water (20 mL). The toluene layer was dried over sodium sulfate (5 g), filtered and concentrated. The remaining oil was stirred with heptane (5 mL) for ten minutes. The stirring was stopped and the heptane was decanted away from the underlying oil. The remaining clear oil was dried under high vacuum for 4 hours. The procedure afforded the mesylate of EHA (0.64 g, 95.8% yield) as colorless oil that solidified after an extended period of time. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.38-4.30 (m, 1H), 4.21 (m, 5H),

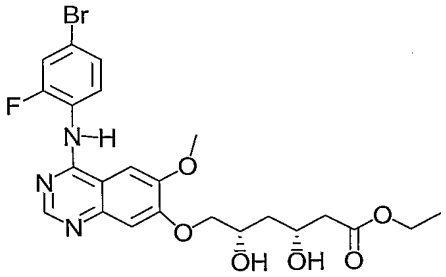
3.05 (s, 3H), 2.55 (dd, 1H, J = 15.6, 6.9 Hz), 2.40 (dd, J = 15.6, 6.0 Hz), 1.63-1.58 (m, 2H), 1.46 (s, 3H), 1.37 (s, 3H), 1.25 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.64, 99.41, 72.37, 67.37, 65.61, 60.84, 41.52, 32.04, 30.04, 14.51.

2-5: (4*R*,6*S*)-{6-[4-(4-Bromo-2-fluorophenylamino)-6-methoxyquinazolin-7-yloxymethyl]-2,2-dimethyl-[1,3]dioxan-4-yl}-acetic acid ethyl ester



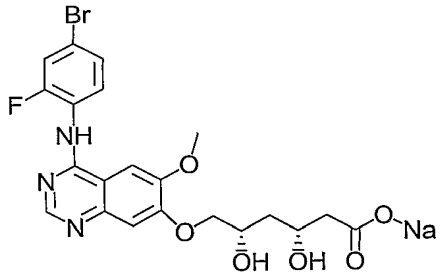
Phenol **2-4** (0.78 g, 2.14 mmol), the mesylate of EHA (0.63 g, 2.02 mmol), and anhydrous potassium carbonate (0.60 g, 4.34 mmol) were added to *N*,*N*-dimethylacetamide (DMA, 5.0 mL) that contained a catalytic amount of 18-crown-6 (2 mg). The mixture was heated to 85-90 °C under an argon atmosphere for 22 hours. After 22 hours, the heating was stopped and the DMA was removed under high vacuum while still warm. The remaining brown solid was purified by flash column chromatography on silica gel (40 g), eluting with 1-10% methanol in dichloromethane. The product containing fractions were combined and concentrated. The remaining orange solid was crystallized from methanol (10 mL). After filtration and drying, the experiment produced **2-5** (0.48 g, 38.7 % yield) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.66 (s, 1H), 8.36 (t, 1H, J = 8.4 Hz), 7.52 (br s, 1H), 7.34-7.24 (m, 3H), 7.08 (s, 1H), 4.45-4.37 (m, 2H), 4.21-3.99 (m, 4H), 3.97 (s, 3H), 2.58 (dd, 1H, J = 15.3, 7.2 Hz), 2.43 (dd, J = 15.3, 5.7 Hz), 1.87-1.79 (m, 2H), 1.51 (s, 3H), 1.37 (s, 3H), 1.27 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.54, 155.42, 154.02, 153.29 (d, J = 245.4 Hz), 152.97, 149.80, 147.19, 127.47, 126.34 (d, J = 12.0 Hz), 124.40, 118.48 (d, J = 23.2 Hz), 115.45 (d, J = 9.0 Hz), 109.25, 108.84, 99.24, 99.10, 71.95, 67.25, 65.35, 60.48, 56.24, 41.38, 33.24, 29.86, 14.21.

2-7: (3*R*,5*S*)-6-[(4-(4-Bromo-2-fluorophenylamino)-6-methoxyquinazolin-7-yl)oxy]-3,5-dihydroxyhexanoic acid ethyl ester



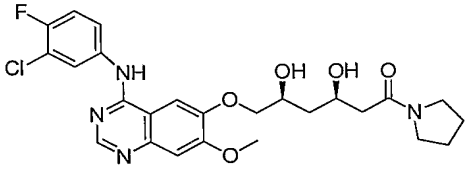
Acetonide **2-5** (0.20 g, 0.345 mmol) was dissolved in tetrahydrofuran (2 mL) and methanol (1 mL) that contained dilute hydrochloric acid (400 µL, 6% HCl). The solution was stirred for 20 hours at room temperature. After 20 hours, saturated sodium bicarbonate solution (5 mL) was added and the product was extracted into diethyl ether (2 × 20 mL). The ether extracts were combined, dried over sodium sulfate (5 g), filtered, and concentrated under reduced pressure. The experiment produced **2-7** (0.17 g, 91.3% yield) as a light yellow solid that was used without further purification for the next step. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (s, 1H), 8.26 (t, 1H, *J* = 8.1 Hz), 7.56 (br s, 1H), 7.30-7.24 (m, 2H), 7.12 (s, 1H), 6.97 (s, 1H), 4.70 (br s, 1H), 4.37 (m, 3H), 4.14 (q, 2H, *J* = 7.0 Hz), 4.03 (m, 2H), 3.88 (s, 3H), 2.52 (m, 2H), 1.80 (m, 2H), 1.24 (t, 3H, *J* = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.30, 155.76, 154.05, 153.68 (d, *J* = 245.7), 152.04, 149.82, 146.97, 127.67, 126.34 (d, *J* = 12.0 Hz), 124.86, 118.78 (d, *J* = 22.6 Hz), 115.95 (d, *J* = 9.0 Hz), 109.34, 108.47, 99.33, 73.04, 69.47, 68.07, 60.99, 56.31, 42.12, 39.01, 14.44.

2-Na: (3*R*,5*S*)-6-{[4-(4-Bromo-2-fluorophenylamino)-6-methoxyquinazolin-7-yl]oxy}-3,5-dihydroxyhexanoic acid, sodium salt



Ester **2-7** (0.17 g, 0.32 mmol) was dissolved in methanol (4 mL) at room temperature. DIUF water (1 mL) containing sodium hydroxide (13.0 mg, 0.33 mmol) was added and the solution was stirred for 3 hours at room temperature. After 3 hours, the methanol/water solution was concentrated. An additional portion of methanol (10 mL) was added and the solution was concentrated. The process was repeated with toluene (10 mL) in order to remove traces of water and methanol. The remaining salt was washed with small volumes of isopropanol (5 mL) and diethyl ether (10 mL). The remaining light yellow salt was dried under high vacuum at room temperature (1 hour) and at 50 °C (3 hours) to remove the bulk of the remaining solvent. The procedure generated **2-Na** (0.16 g, 95.4% yield) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.70 (br s, 1H), 8.29 (s, 1H), 7.80 (s, 1H), 7.60 (d, 1H, *J* = 9.6 Hz), 7.52 (t, 1H, *J* = 8.4 Hz), 7.42 (d, 1H, *J* = 8.4 Hz), 7.27 (br s, 1H), 7.14 (s, 1H), 5.16 (br s, 1H), 4.10-3.80 (m, 7H), 2.10 (dd, 1H, *J* = 15.3, 3.9 Hz), 1.91 (dd, 1H, *J* = 15.3, 8.7 Hz), 1.58 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 17.31, 156.86, 156.40 (d, *J* = 249.6 Hz), 153.48, 152.80, 148.62, 146.59, 129.12, 127.78 (d, *J* = 12.0 Hz), 127.15 (d, *J* = 3 Hz), 118.96 (d, *J* = 23.8 Hz), 116.34 (d, *J* = 9.0 Hz), 109.10, 107.49, 102.36, 73.03, 66.51, 65.88, 55.97, 43.69, 41.15.

Example 3: (3*R*,5*S*)-6-{[4-(3-Chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]oxy}-3,5-dihydroxy-1-(pyrrolidin-1-yl)-hexan-1-one.



The synthesis of the amide derivatives of Example **1** is shown in Scheme **3** below:

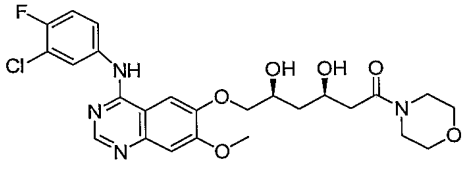
1-Na **3-2**

Scheme 3

An amine (3 equiv) was added to a solution of Compound **1-Na** (1 equiv), EDC (5 equiv), HOBt (5 equiv), and DIEA (5 equiv) in DMF. After the solution was stirred at 25 °C overnight (stirred at 55 °C for a couple of hours if necessary), DMF was removed via evaporation under reduced pressure. The resulting residue was suspended in ethyl acetate, washed by saturated $NaHCO_3$ (3x) and brine (3x), and dried over Na_2SO_4. The ethyl acetate was removed under vacuum to give the crude product. This crude material was subjected to preparative HPLC to give the final product amide, which was subsequently characterized by LC-MS and NMR spectroscopy.

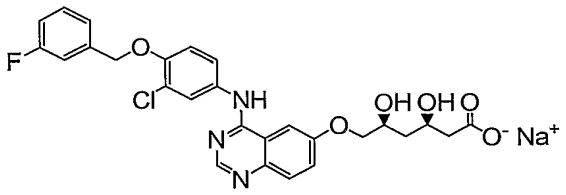
Synthesis of (3*R*,5*S*)-6-{[4-(3-Chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]oxy}-3,5-dihydroxy-1-(pyrrolidin-1-yl)-hexan-1-one. An amount of 55 mg (92%) product was obtained after preparative HPLC from 70 mg (0.143 mmol) of Compound **1-Na**. LC-MS: single peak at 254 nm, MH^+ calcd for $C_{25}H_{28}ClFN_4O_5$: 519, obtained: 519. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 8.49 (s, 1H), 8.12 (dd, *J* = 3.2 Hz, *J* = 7.2 Hz, 1H), 7.82 (s, 1H), 7.78 (m, 1H), 7.44 (t, *J* = 9.2 Hz, 1H), 7.20 (s, 1H), 5.09 (s, 2H), 4.86 (s, 1H), 4.20-4.00 (m, 4H), 3.93 (s, 3H), 3.43 (m, 2H), 3.28-3.15 (m, 4H), 2.40 (m, 2H), 1.88-1.62 (m, 4H).

Example 4: (3*R*,5*S*)-6-{[4-(3-Chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl]oxy}-3,5-dihydroxy-1-(morpholin-4-yl)-hexan-1-one.



An amount of 23 mg (60%) product was obtained after preparative HPLC from 35 mg (0.072 mmol) of Compound **1-Na**. LC-MS: single peak at 254 nm, MH^+ calcd for $C_{25}H_{28}ClFN_4O_6$: 535, obtained: 535. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 8.48 (s, 1H), 8.11 (dd, *J* = 2.8 Hz, *J* = 6.8 Hz, 1H), 7.80 (s, 1H), 7.77 (m, 1H), 7.43 (t, *J* = 9.2 Hz, 1H), 7.20 (s, 1H), 5.06 (s, 1H), 4.82 (s, 1H), 4.12 (m, 2H), 4.05 (m, 2H), 3.93 (s, 3H), 3.60-3.40 (m, 8H), 2.58-2.40 (m, 2H, buried in the DMSO signals), 1.82-1.64 (m, 2H).

Example 5: Sodium; (3R,5S)-6-{(4-[3-chloro-4-(3-fluorobenzyloxy) phenylamino]-quinazolin-6-yl)oxy}-3,5-dihydroxy hexanoate



Step A: ((4R,6S)-6-{(4-[3-Chloro-4-(3-fluorobenzyloxy)phenylamino]-quinazolin-6-yl)oxymethyl}-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid *tert*-butyl ester

To a mixture of 4-[3-Chloro-4-(3-fluorobenzyloxy)phenylamino]-quinazolin-6-ol (300 mg, 0.76 mmol) and cesium carbonate (491 mg, 1.5 mmol) in DMAC (4 mL) was added ((4R,6S)-2,2-dimethyl-6-trifluoromethanesulfonyloxymethyl-[1,3]dioxan-4-yl)-acetic acid *tert*-butyl ester (243 mg, 0.84 mol). The mixture was stirred at rt for 18 h, and then diluted with EtOAc. The mixture was filtered through a plug of SiO_2 and concentrated. The crude residue was purified by silica gel chromatography (ethyl acetate/hexanes) to afford 200 mg of the title compound as a pale yellow oil which was used without further purification. HPLC:MS 638.2 (M+H).

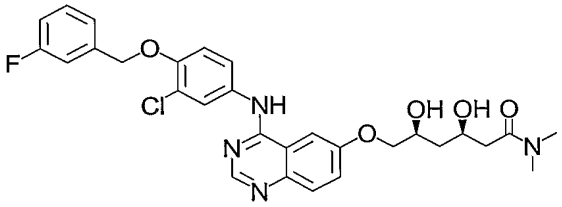
Step B: (4R,6S)-6-{(4-[3-Chloro-4-(3-fluorobenzyloxy)phenylamino]-quinazolin-6-yl)oxymethyl}-4-hydroxy-tetrahydropyran-2-one

To a solution of the product from Step A (275 mg, 0.43 mmol) in CH_2Cl_2 (1 mL) was added 5 mL of TFA. The reaction was aged at rt until the starting material was consumed as judged by HPLC analysis. The reaction was concentrated and then azeotroped with toluene to give a yellow oil which was used without further purification. HPLC:MS 542.2 (M+H).

Step C: Sodium; (3R,5S)-6-{(4-[3-chloro-4-(3-fluorobenzyloxy)phenylamino]-quinazolin-6-yl)oxy}-3,5-dihydroxyhexanoate

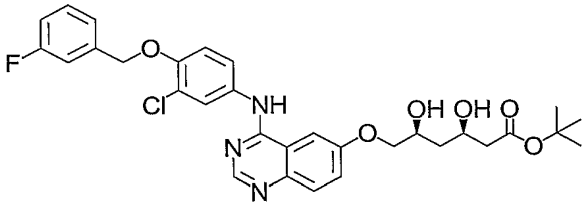
To a solution of the product from Step B in THF (3 mL) at rt was added 3 mL of 1M NaOH. When the reaction was judged complete by HPLC analysis, the reaction was acidified with 2M HCl until a pH ~4 was reached. The crude reaction mixture was concentrated to remove the organics, diluted with DMSO, and purified by reverse-phase preparative HPLC to give the TFA salt of the dihydroxyacid contaminated with the corresponding δ-lactone. To this residue in THF was added 1M NaOH (2 eq). The resulting solution was stirred for 30 min, purged with CO_2, concentrated to remove the THF and then frozen and lyophilized to give the title compound as a yellow solid homogeneous by HPLC analysis. HPLC:MS 542.2 (M+H).

Example 6: (3R,5S)-6-{(4-[3-Chloro-4-(3-fluorobenzyloxy)phenylamino]-quinazolin-6-yl)oxy}-3,5-dihydroxy-hexanoic acid dimethylamide



To a solution of the product from Example 5, Step B was added Me_2NH (2M in MeOH, 10 mL). After 18 h, the solution was concentrated *in vacuo* and the crude residue was purified by reverse-phase preparative HPLC to give the title compound as a pale yellow solid. HPLC:MS 569.3 (M+H).

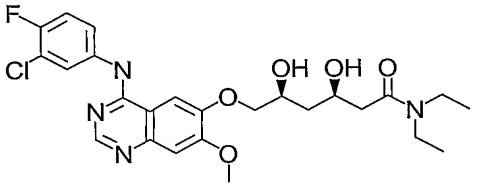
Example 7: (3R,5S)-6-{(4-[3-Chloro-4-(3-fluorobenzyloxy)phenylamino]-quinazolin-6-yl)oxy}-3,5-dihydroxyhexanoic acid *tert*-butyl ester



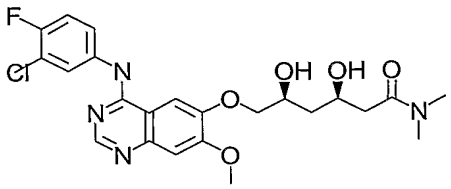
To a solution of the product from Example 5, Step A in THF was added 1M HCl. After 3 h, the solution was purified by reverse-phase preparative HPLC to give the title compound as a bright yellow solid. HPLC:MS 598.2 (M+H).

Example 8: Further amide derivatives of Example 1

The following derivatives can be made utilizing the above procedures.



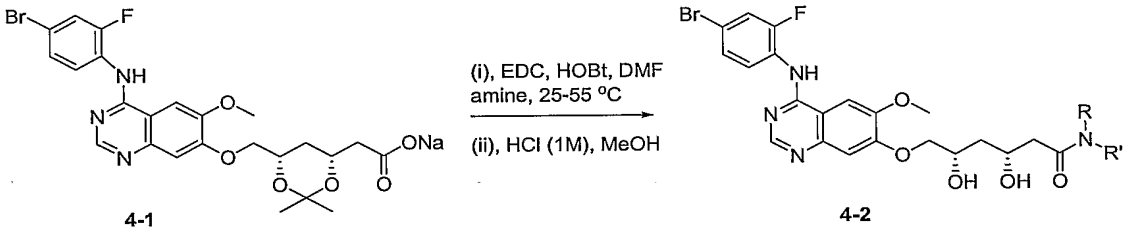
8a



8b

Example 9: Amide derivatives of Example 2

The synthesis of the amide derivatives of Example **2** is described in Scheme **4** below:

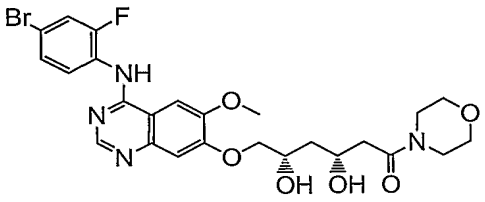


4-1 **4-2**

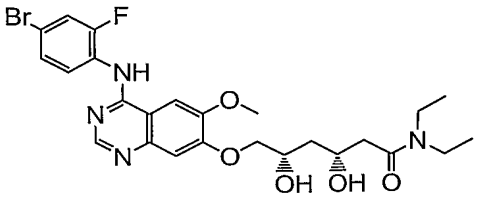
Scheme 4

An amine (3 equiv) was added to a solution of Compound **4-1** (1 equiv), EDC (5 equiv), HOBt (5 equiv), and DIEA (5 equiv) in DMF. After the solution was stirred at 25 °C overnight (stirred at 55 °C for a couple of hours if necessary), DMF was removed via evaporation under reduced pressure. The resulting residue was suspended in ethyl acetate, washed by saturated $NaHCO_3$ (3x) and brine (3x), and dried over Na_2SO_4. The ethyl acetate was removed under vacuum to give the amide crude product. This crude material was treated with HCl (1M) in MeOH for 1h at 25 °C to remove the acetonide, and the reaction mixture was directly subjected to preparative HPLC to give the final product dihydroxy amide, which was subsequently characterized by LC-MS and NMR spectroscopy.

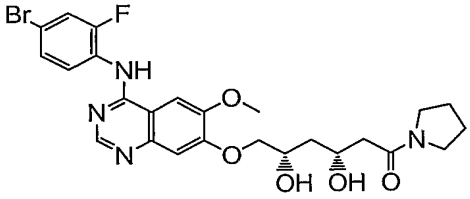
Following the procedure above, amides **9a-f** can be made by those skilled in the art.



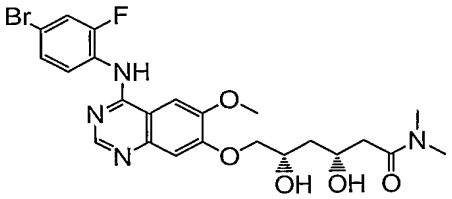
9a



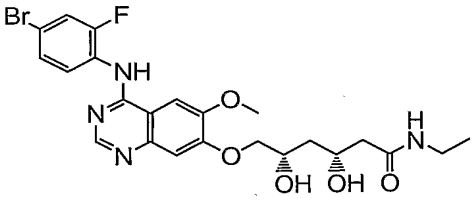
9b



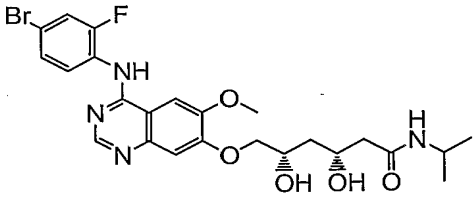
9c



9d

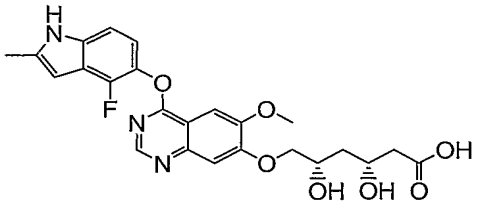


9e

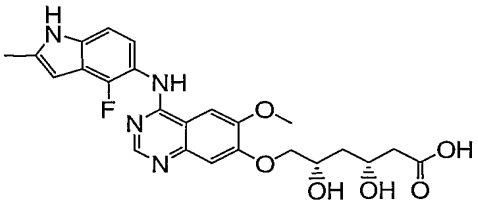


9f

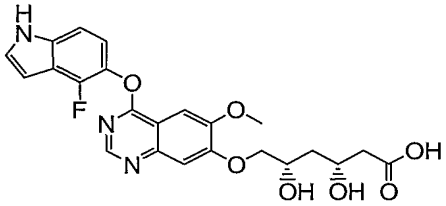
Example 10. Following the above procedures and known procedures in the literature, the following examples **10a-j** can be made.



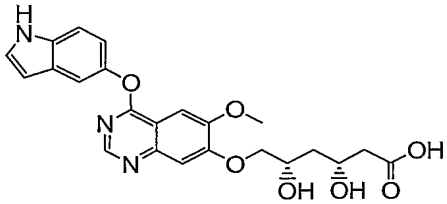
10a



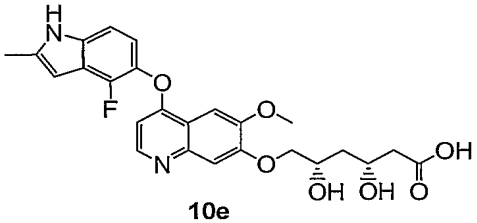
10b



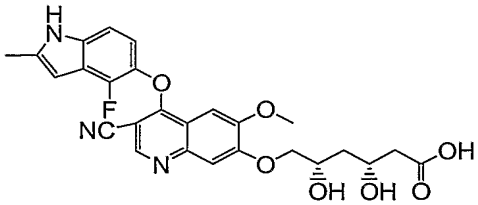
10c



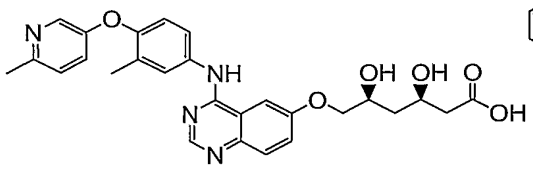
10d



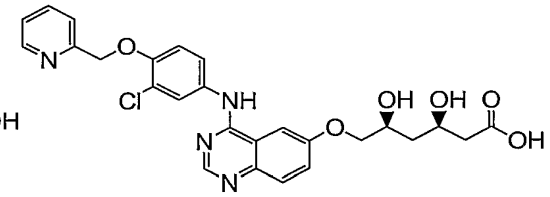
10e



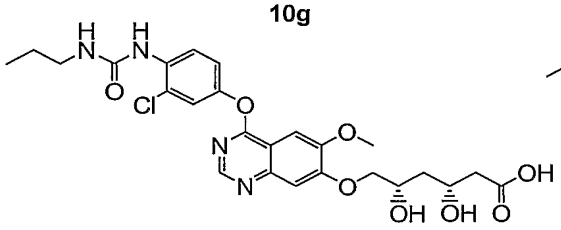
10f



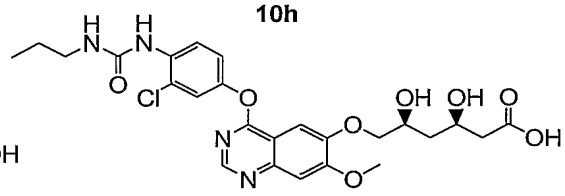
10g



10h

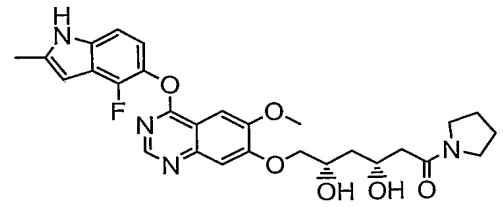


10i

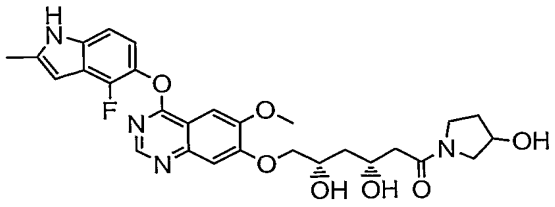


10j

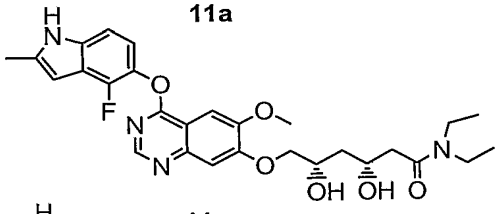
Example 11. Amide derivatives of Example **10** are illustrated using derivatives of **10a** below:



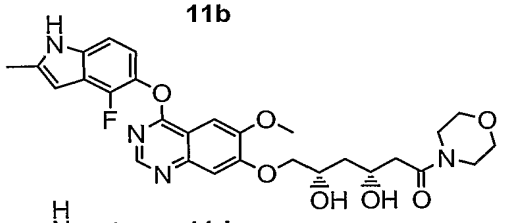
11a



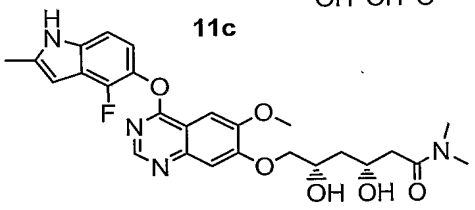
11b



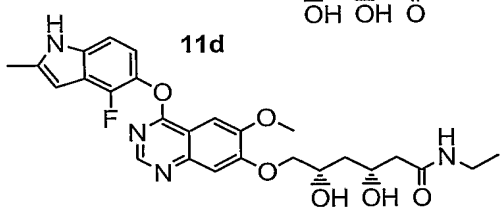
11c



11d

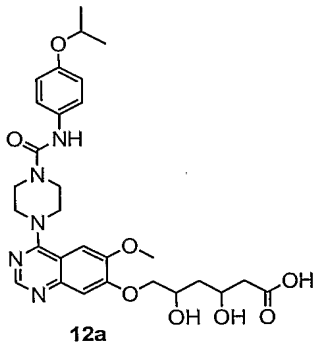


11e

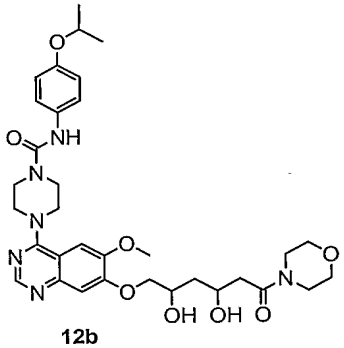


11f

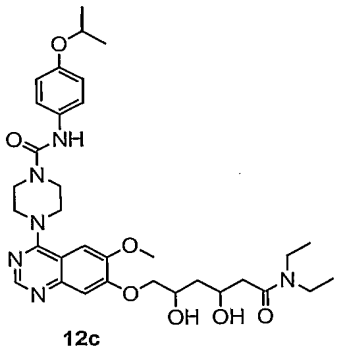
Example 12. Following the above procedures and known procedures in the 3literature, the following examples **12a-f** can be made.



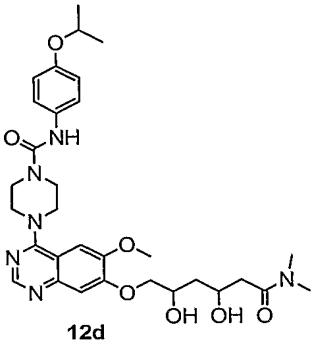
12a



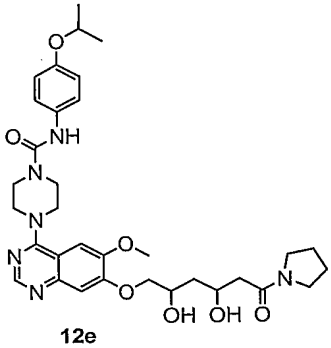
12b



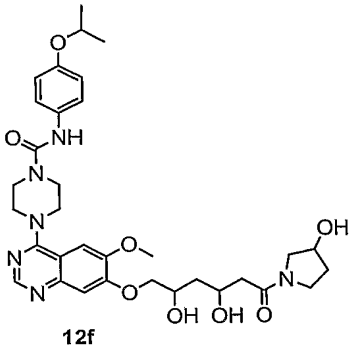
12c



12d



12e

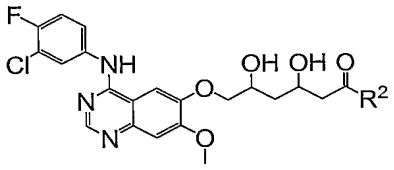


12f

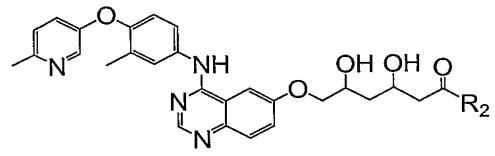
5

Further Examples:

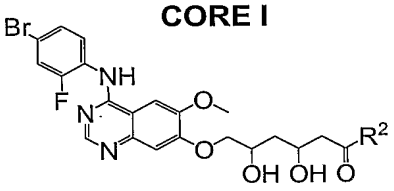
Examples 16 – 565: Still further amide examples are shown in the following table:



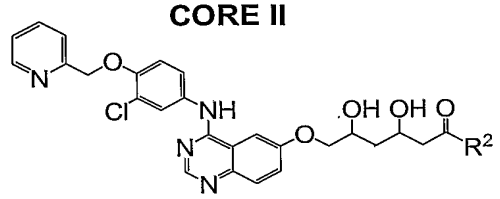
CORE I



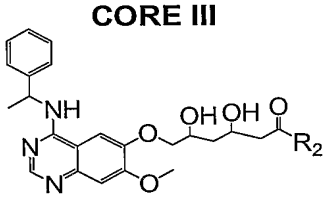
CORE II



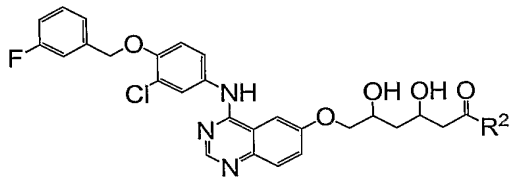
CORE III



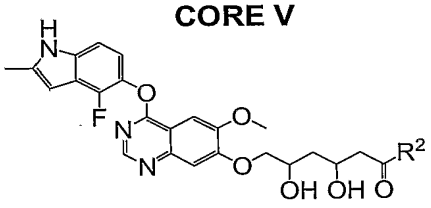
CORE IV



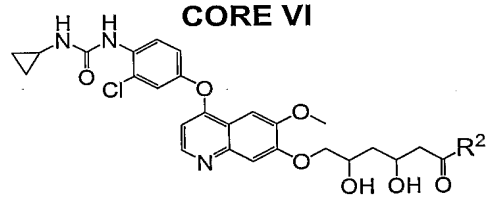
CORE V



CORE VI

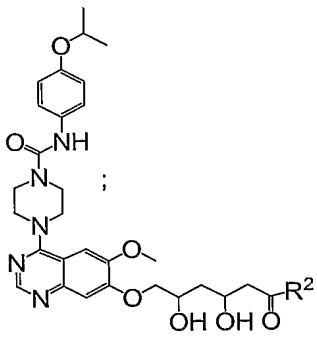


CORE VII

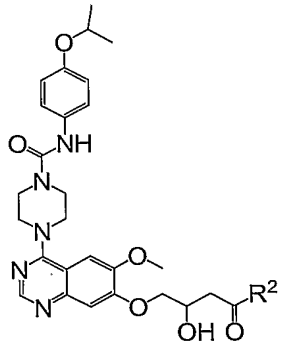


CORE VIII

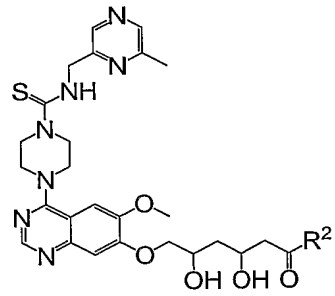
5



CORE IX



CORE X



CORE XI

Ex#	Core	R^2	Ex#	Core	R^2	Ex#	Core	R^2
16	I	a	66	II	a	116	III	a
17	I	b	67	II	b	117	III	b
18	I	c	68	II	c	118	III	c
19	I	d	69	II	d	119	III	d
20	I	e	70	II	e	120	III	e
21	I	f	71	II	f	121	III	f
22	I	g	72	II	g	122	III	g
23	I	h	73	II	h	123	III	h
24	I	i	74	II	i	124	III	i
25	I	j	75	II	j	125	III	j
26	I	k	76	II	k	126	III	k
27	I	l	77	II	l	127	III	l
28	I	m	78	II	m	128	III	m
29	I	n	79	II	n	129	III	n
30	I	o	80	II	o	130	III	o
31	I	p	81	II	p	131	III	p
32	I	q	82	II	q	132	III	q
33	I	r	83	II	r	133	III	r
34	I	s	84	II	s	134	III	s
35	I	t	85	II	t	135	III	t
36	I	u	86	II	u	136	III	u
37	I	v	87	II	v	137	III	v
38	I	w	88	II	w	138	III	w
39	I	x	89	II	x	139	III	x
40	I	y	90	II	y	140	III	y
41	I	z	91	II	z	141	III	z
42	I	aa	92	II	aa	142	III	aa
43	I	ab	93	II	ab	143	III	ab
44	I	ac	94	II	ac	144	III	ac
45	I	ad	95	II	ad	145	III	ad
46	I	ae	96	II	ae	146	III	ae
47	I	af	97	II	af	147	III	af
48	I	ag	98	II	ag	148	III	ag
49	I	ah	99	II	ah	149	III	ah
50	I	ai	100	II	ai	150	III	ai
51	I	aj	101	II	aj	151	III	aj
52	I	ak	102	II	ak	152	III	ak
53	I	al	103	II	al	153	III	al
54	I	am	104	II	am	154	III	am
55	I	an	105	II	an	155	III	an
56	I	ao	106	II	ao	156	III	ao
57	I	ap	107	II	ap	157	III	ap
58	I	aq	108	II	aq	158	III	aq
59	I	ar	109	II	ar	159	III	ar

Ex#	Core	R^2	Ex#	Core	R^2	Ex#	Core	R^2
60	I	as	110	II	as	160	III	as
61	I	at	111	II	at	161	III	at
62	I	au	112	II	au	162	III	au
63	I	av	113	II	av	163	III	av
64	I	aw	114	II	aw	164	III	aw
65	I	ax	115	II	ax	165	III	ax

Ex#	Core	R^2	Ex#	Core	R^2	Ex#	Core	R^2
166	IV	a	216	V	a	266	VI	a
167	IV	b	217	V	b	267	VI	b
168	IV	c	218	V	c	268	VI	c
169	IV	d	219	V	d	269	VI	d
170	IV	e	220	V	e	270	VI	e
171	IV	f	221	V	f	271	VI	f
172	IV	g	222	V	g	272	VI	g
173	IV	h	223	V	h	273	VI	h
174	IV	i	224	V	i	274	VI	i
175	IV	j	225	V	j	275	VI	j
176	IV	k	226	V	k	276	VI	k
177	IV	l	227	V	l	277	VI	l
178	IV	m	228	V	m	278	VI	m
179	IV	n	229	V	n	279	VI	n
180	IV	o	230	V	o	280	VI	o
181	IV	p	231	V	p	281	VI	p
182	IV	q	232	V	q	282	VI	q
183	IV	r	233	V	r	283	VI	r
184	IV	s	234	V	s	284	VI	s
185	IV	t	235	V	t	285	VI	t
186	IV	u	236	V	u	286	VI	u
187	IV	v	237	V	v	287	VI	v
188	IV	w	238	V	w	288	VI	w
189	IV	x	239	V	x	289	VI	x
190	IV	y	240	V	y	290	VI	y
191	IV	z	241	V	z	291	VI	z
192	IV	aa	242	V	aa	292	VI	aa
193	IV	ab	243	V	ab	293	VI	ab
194	IV	ac	244	V	ac	294	VI	ac
195	IV	ad	245	V	ad	295	VI	ad
196	IV	ae	246	V	ae	296	VI	ae
197	IV	af	247	V	af	297	VI	af
198	IV	ag	248	V	ag	298	VI	ag
199	IV	ah	249	V	ah	299	VI	ah

Ex#	Core	R^2	Ex#	Core	R^2	Ex#	Core	R^2
200	IV	ai	250	V	ai	300	VI	ai
201	IV	aj	251	V	aj	301	VI	aj
202	IV	ak	252	V	ak	302	VI	ak
203	IV	al	253	V	al	303	VI	al
204	IV	am	254	V	am	304	VI	am
205	IV	an	255	V	an	305	VI	an
206	IV	ao	256	V	ao	306	VI	ao
207	IV	ap	257	V	ap	307	VI	ap
208	IV	aq	258	V	aq	308	VI	aq
209	IV	ar	259	V	ar	309	VI	ar
210	IV	as	260	V	as	310	VI	as
211	IV	at	261	V	at	311	VI	at
212	IV	au	262	V	au	312	VI	au
213	IV	av	263	V	av	313	VI	av
214	IV	aw	264	V	aw	314	VI	aw
215	IV	ax	265	V	ax	315	VI	ax

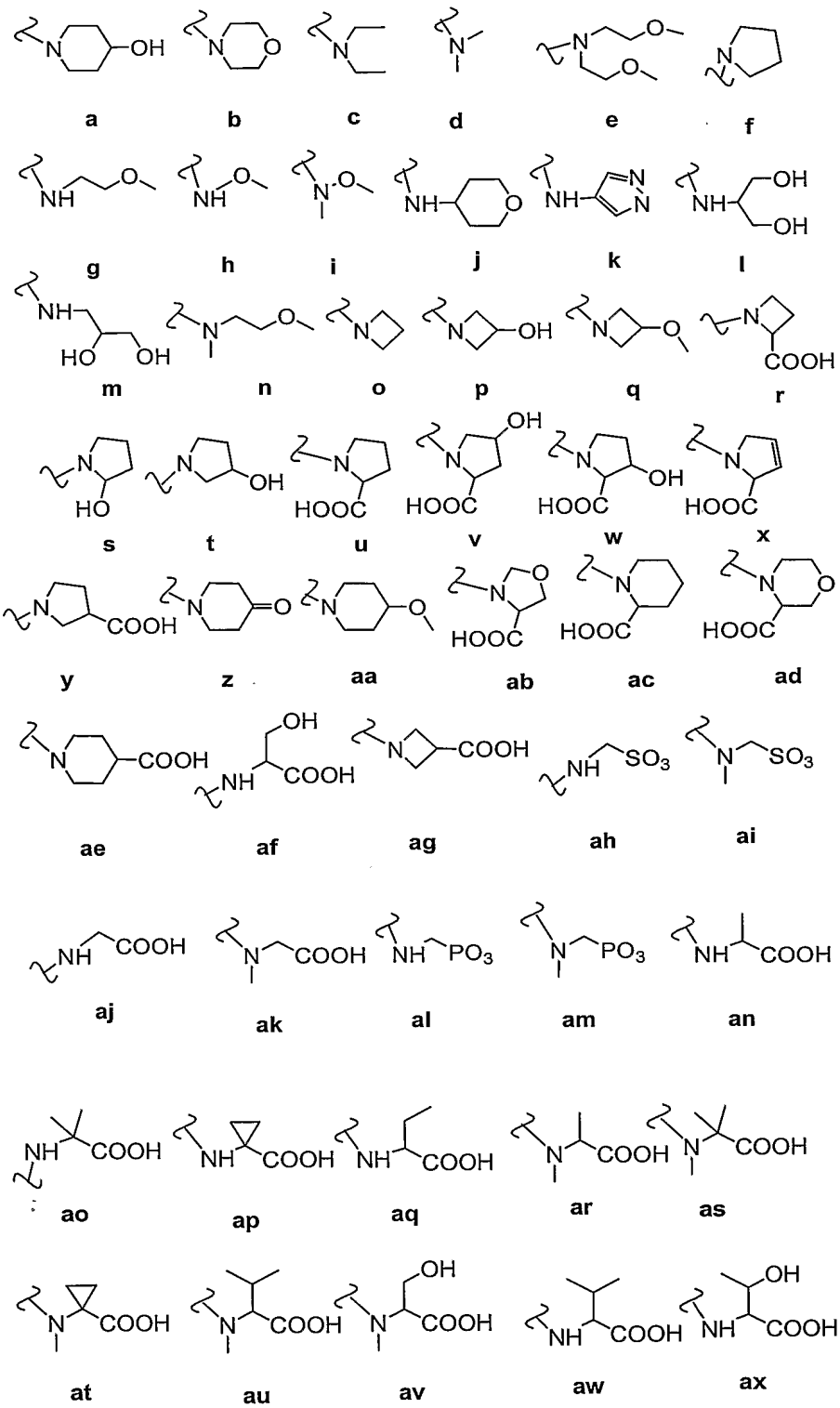
Ex#	Core	R^2	Ex#	Core	R^2	Ex#	Core	R^2
316	VII	a	366	VIII	a	416	IX	a
317	VII	b	367	VIII	b	417	IX	b
318	VII	c	368	VIII	c	418	IX	c
319	VII	d	369	VIII	d	419	IX	d
320	VII	e	370	VIII	e	420	IX	e
321	VII	f	371	VIII	f	421	IX	f
322	VII	g	372	VIII	g	422	IX	g
323	VII	h	373	VIII	h	423	IX	h
324	VII	i	374	VIII	i	424	IX	i
325	VII	j	375	VIII	j	425	IX	j
326	VII	k	376	VIII	k	426	IX	k
327	VII	l	377	VIII	l	427	IX	l
328	VII	m	378	VIII	m	428	IX	m
329	VII	n	379	VIII	n	429	IX	n
330	VII	o	380	VIII	o	430	IX	o
331	VII	p	381	VIII	p	431	IX	p
332	VII	q	382	VIII	q	432	IX	q
333	VII	r	383	VIII	r	433	IX	r
334	VII	s	384	VIII	s	434	IX	s
335	VII	t	385	VIII	t	435	IX	t
336	VII	u	386	VIII	u	436	IX	u
337	VII	v	387	VIII	v	437	IX	v
338	VII	w	388	VIII	w	438	IX	w
339	VII	x	389	VIII	x	439	IX	x
340	VII	y	390	VIII	y	440	IX	y

Ex#	Core	R^2	Ex#	Core	R^2	Ex#	Core	R^2
341	VII	z	391	VIII	z	441	IX	z
342	VII	aa	392	VIII	aa	442	IX	aa
343	VII	ab	393	VIII	ab	443	IX	ab
344	VII	ac	394	VIII	ac	444	IX	ac
345	VII	ad	395	VIII	ad	445	IX	ad
346	VII	ae	396	VIII	ae	446	IX	ae
347	VII	af	397	VIII	af	447	IX	af
348	VII	ag	398	VIII	ag	448	IX	ag
349	VII	ah	399	VIII	ah	449	IX	ah
350	VII	ai	400	VIII	ai	450	IX	ai
351	VII	aj	401	VIII	aj	451	IX	aj
352	VII	ak	402	VIII	ak	452	IX	ak
353	VII	al	403	VIII	al	453	IX	al
354	VII	am	404	VIII	am	454	IX	am
355	VII	an	405	VIII	an	455	IX	an
356	VII	ao	406	VIII	ao	456	IX	ao
357	VII	ap	407	VIII	ap	457	IX	ap
358	VII	aq	408	VIII	aq	458	IX	aq
359	VII	ar	409	VIII	ar	459	IX	ar
360	VII	as	410	VIII	as	460	IX	as
361	VII	at	411	VIII	at	461	IX	at
362	VII	au	412	VIII	au	462	IX	au
363	VII	av	413	VIII	av	463	IX	av
364	VII	aw	414	VIII	aw	464	IX	aw
365	VII	ax	415	VIII	ax	465	IX	ax

E3x#	Core	R^2	Ex#	Core	R^2
466	X	a	516	XI	a
467	X	b	517	XI	b
468	X	c	518	XI	c
469	X	d	519	XI	d
470	X	e	520	XI	e
471	X	f	521	XI	f
472	X	g	522	XI	g
473	X	h	523	XI	h
474	X	i	524	XI	i
475	X	j	525	XI	j
476	X	k	526	XI	k
477	X	l	527	XI	l
478	X	m	528	XI	m
479	X	n	529	XI	n
480	X	o	530	XI	o
481	X	p	531	XI	p

Ex#	Core	R^2	Ex#	Core	R^2
482	X	q	532	XI	q
483	X	r	533	XI	r
484	X	s	534	XI	s
485	X	t	535	XI	t
486	X	u	536	XI	u
488	X	w	538	XI	w
489	X	x	539	XI	x
490	X	y	540	XI	y
491	X	z	541	XI	z
492	X	aa	542	XI	aa
493	X	ab	543	XI	ab
494	X	ac	544	XI	ac
495	X	ad	545	XI	ad
496	X	ae	546	XI	ae
497	X	af	547	XI	af
498	X	ag	548	XI	ag
499	X	ah	549	XI	ah
500	X	ai	550	XI	ai
501	X	aj	551	XI	aj
502	X	ak	552	XI	ak
553	X	al	553	XI	al
504	X	am	554	XI	am
505	X	an	555	XI	an
506	X	ao	556	XI	ao
507	X	ap	557	XI	ap
508	X	aq	558	XI	aq
509	X	ar	559	XI	ar
510	X	as	560	XI	as
511	X	at	561	XI	at
512	X	au	562	XI	au
513	X	av	563	XI	av
514	X	aw	564	XI	aw
515	X	ax	565	XI	ax

In the above table, R^2 is selected from the following radicals:



These amide examples **16 - 565** can be made by those skilled in the art following the above procedure and/or known procedures.

The compounds described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

Utility:

The present invention provides compounds capable of regulating and/or modulating protein kinase activities of, but not limited to, VEGFR (Vascular Endothelial Growth Factor Receptor), EGFR (Epidermal Growth Factor Receptor), FGFR (Fibroblast Growth Factor Receptor) or PDGFR (Platelate Derived Growth Factor Receptor). Thus, the present invention provides a therapeutic approach to the treatment of disorders related to the abnormal functioning of these kinases. Such disorders include, but not limited to, solid tumors such as glioblastoma, melanoma, and Kaposi's sarcoma, and ovarian, lung, prostate, pancreatic, colon and epidermoid carcinoma. In addition, VEGFR/FGFR inhibitors may also be used in the treatment of restenosis and diabetic retinopathy.

Furthermore, this invention relates to the inhibition of vasculogenesis and angiogenesis by receptor-mediated pathways, including the pathways comprising VEGF receptors, and/or FGF receptors. Thus the present invention provides therapeutic approaches to the treatment of cancer and other diseases that involve the uncontrolled formation of blood vessels.

VEGFR Biochemical Assay

The compounds were assayed for biochemical activity by Upstate Ltd at Dundee, United Kingdom, according to the following procedure. In a final reaction volume of 25 μl, KDR (h) (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 0.33 mg/ml myelin basic protein, 10 mM MgAcetate and [γ-^{33}P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 40

minutes at room temperature, the reaction is stopped by the addition of 5 μl of a 3% phosphoric acid solution. 10 μl of the reaction is then spotted onto a P30 filtermat and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

EGFR biochemical assay

The compounds were assayed for biochemical activity by Upstate Ltd at Dundee, United Kingdom, according to the following procedure. In a final reaction volume of 25 μl, EGFR (h) (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 10 mM $MnCl_2$, 0.1 mg/ml poly(Glu, Tyr) 4:1, 10 mM MgAcetate and [γ-^{33}P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 5 μl of a 3% phosphoric acid solution. 10 μl of the reaction is then spotted onto a filtermat A and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

Cellular Assay: HUVEC: VEGF induced proliferation

The compounds were assayed for cellular activity in the VEGF induced proliferation of HUVEC cells. HUVEC cells (Cambrex, CC-2517) were maintained in EGM (Cambrex, CC-3124) at 37°C and 5% CO_2. HUVEC cells were plated at a density 5000 cells/well (96 well plate) in EGM. Following cell attachment (1hour) the EGM-medium was replaced by EBM (Cambrex, CC-3129) + 0.1% FBS (ATTC , 30-2020) and the cells were incubated for 20 hours at 37°C. The medium was replaced by EBM +1% FBS, the compounds were serial diluted in DMSO and added to the cells to a final concentration of 0 – 5,000 nM and 1% DMSO. Following a 1 hour pre-incubation at 37°C cells were stimulated with 10ng/ml VEGF (Sigma, V7259) and incubated for 45 hours at 37°C. Cell proliferation was measured by BrdU DNA incorporation for 4 hours and BrdU label was quantitated by ELISA (Roche kit, 16472229) using 1M

H_2SO_4 to stop the reaction. Absorbance was measured at 450nm using a reference wavelength at 690nm.

Detailed Description of Figures:

Figure 1 is a scheme showing the synthesis of the 6-(omega alkanoic acid) quinazolines from 6,7-dimethoxy-3,4-dihydroquinazolin-4-one. The acid-promoted deprotection of the 6-hydroxy group of the quinazoline went according to the procedure in WO96/33980. Routine acetylation of the revealed hydroxyl was carried out in refluxing acetic anhydride/pyridine to give compound **1-3**. The amide group of the quinazolin-4-one was converted to the chloroimine to give 6-acetoxy-4-chloro-7-methoxyquinazoline as the hydrochloride salt. Overall yield for the two steps was 82%. The 4-chloro-quinazoline **1-4** was converted to the aniline derivative by displacement of the chloride to give **1-5** in good yield by reaction with 3-chloro-4-fluoroaniline. The acetyl group is removed by reaction with ammonium hydroxide in refluxing methanol to provide **1-6** in 90% yield. The hydroxyl group of **1-6** was deprotonated with potassium carbonate in dimethyl acetamide and a catalytic amount of 18-crown-6 ether and alkylated with primary mesylate **1b** to give **1-7** in adequate yield according to the procedure of Jendrella, H.; et al. *J. Med. Chem.* **1991**, *34*, 2962-2983. The acetonide protecting group was removed in acidic ethanol/THF to provide **1-8** in 46% yield. Saponification of the ester to the sodium salt **1-Na** was done with sodium hydroxide in aqueous methanol at room temperature.

Figure 2 is a scheme showing the synthesis of **2-Na**, which is the 7-(omega alkanoic acid) quinazoline derivative, from 7-benzyloxy-4-chloro-6-methoxyquinzoline. This starting material was purchased from J.W. Pharmlab. The first reaction is an S_NAr-type displacement of chloride from **2-2** with an excess of 4-bromo-2-fluoroaniline in refluxing isopropanol to give the aniline derivative **2-3** in 45% yield. This was dissolved in trifluoroacetic acid and refluxed for 1.5 hours to provide the debenzylated **2-4** in 99% yield. The 7-hydroxyquinazoline **2-4** was treated with an excess of potassium carbonate in dimethylacetamide in the presence of a catalytic amount of 18-crown-6 ether at 85-90 °C for 22 hours. There was obtained approximately 39% of a light yellow

solid, **2-5**. Standard acetonide deprotection conditions have the dihydroxy ethyl ester **2-7** in 91% yield. A stoichiometric amount of sodium hydroxide in aqueous methanol hydrolyzed the ester to provide the sodium salt, **2-Na** in 95% yield. Legend of scheme: A) isopropanol, 90 °C; B) TFA, reflux; C) K_2CO_3, 90 °C; D) THF, 5% HCl; E) methanol, water, NaOH (1 equivalent).

Figure 3A is a table of preferred compounds of the invention. All of the compounds shown have at least one asymmetric center and the stereochemistry at any given asymmetric center is *RS*, *R*, or *S*.

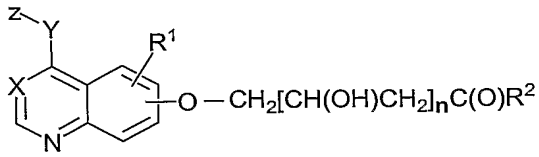
Figure 3B is a table of preferred compounds of the invention. All of the compounds shown have at least one asymmetric center and the stereochemistry at any given asymmetric center is *RS*, *R*, or *S*.

Figure 3C is a table of preferred compounds of the invention. All of the compounds shown have at least one asymmetric center and the stereochemistry at any given asymmetric center is *RS*, *R*, or *S*.

Figure 4 is a table of preferred compounds of the invention. All of the compounds shown have at least one asymmetric center and the stereochemistry at any given asymmetric center is *RS*, *R*, or *S*. These compounds differ from those in Figures 3 in that they have a piperazine ring directly bonded to the quinazoline ring.

What is claimed is:

1. A compound of Formula (**I**):



(Formula I)

wherein:

X is a triradical selected from the group consisting of N and C(R^3);

Y is a diradical selected from the group consisting of N(R^4) and O;

Z is a radical selected from the group consisting of optionally substituted phenyl, pyridine, indole, indazole, naphthalene, benzofuran, and benzothiophene;

R^1 is a radical selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) alkoxy, (C3-C8) cycloalkoxy, and (C5-C8) heterocycloalkoxy;

R^2 is a radical selected from the group consisting of hydroxyl, (C1-C6) alkoxy, (C5-C8) cycloalkoxy, and -NR^5R^6;

n is 1 or 2;

R^3 is a radical selected from the group consisting of hydrogen and nitrile;

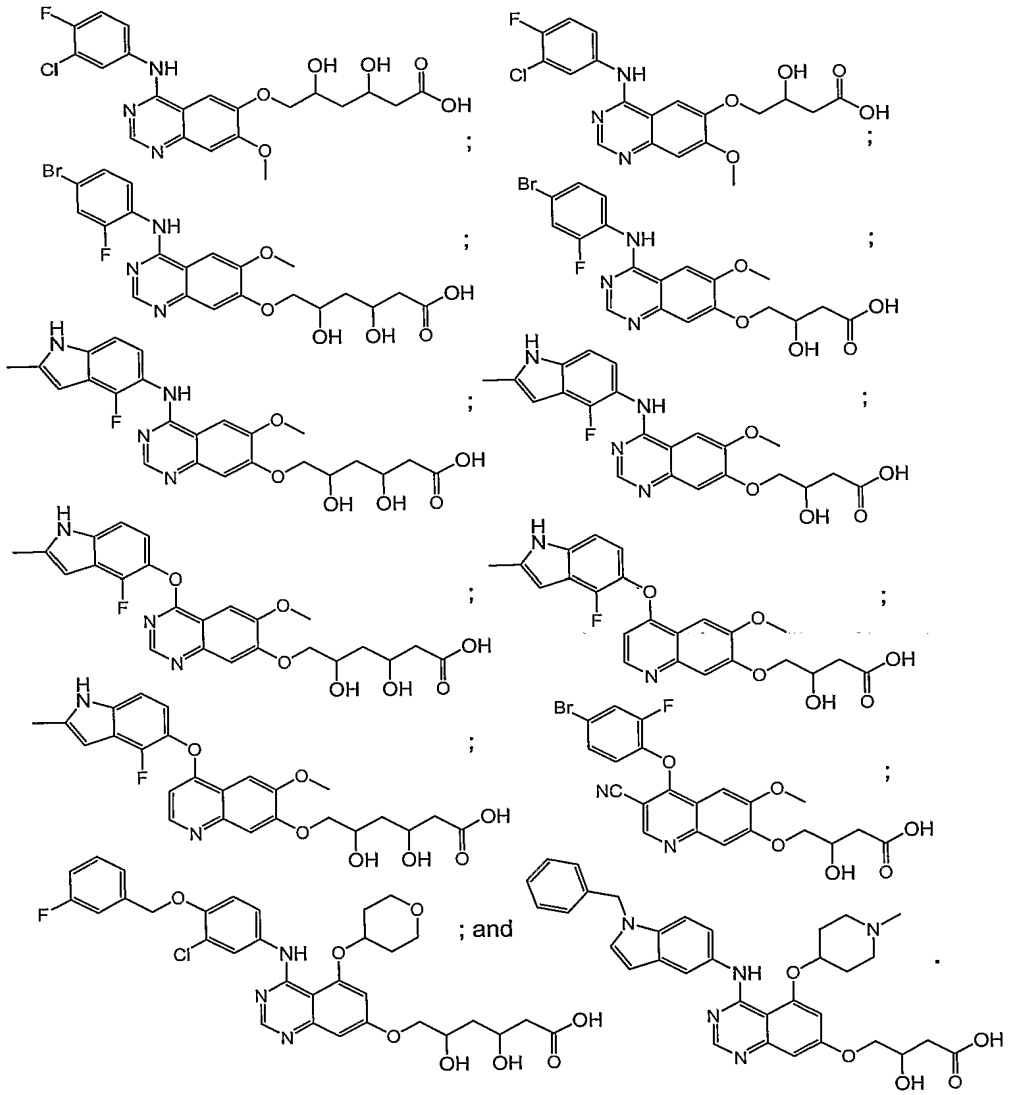
R^4 is a radical selected from the group consisting of hydrogen and (C1-C6) alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C1-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C1-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphoric acid, (C1-C6) alkyl sulfuric acid, (C1-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C10) aryl, (C5-C9) heteroaryl, (C3-C8) cycloalkyl carboxylic acid; or R^5 and R^6 together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids; or NR^5R^6 may form a cyclic ring containing 0-3 additional heteroatoms selected from N, O, or S;

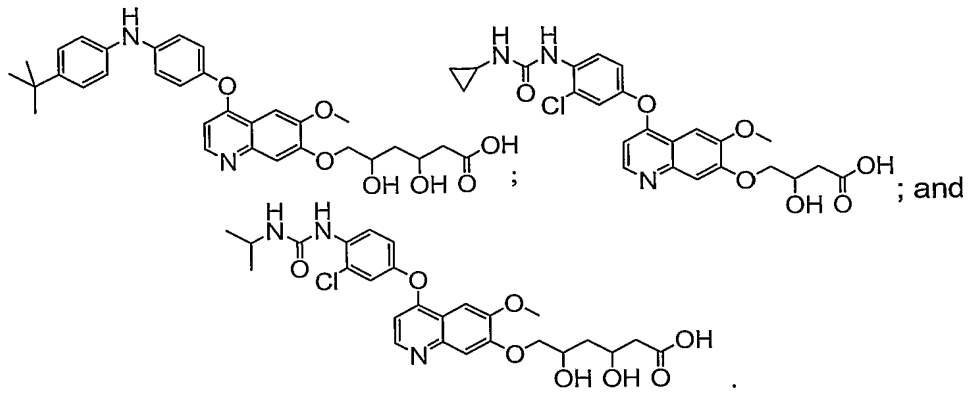
or, a pharmaceutically acceptable salt, its tautomer, a pharmaceutically acceptable salt of its tautomer, or a prodrug thereof.

2. The compound, salt, tautomer, or prodrug according to claim 1 wherein R^2 is a radical selected from the group consisting of hydroxyl, (C1-C6) alkoxy, and (C5-C8) cycloalkoxy.

3. The compound or salt of claim 2, wherein the compound is selected from the group represented by the following structures:



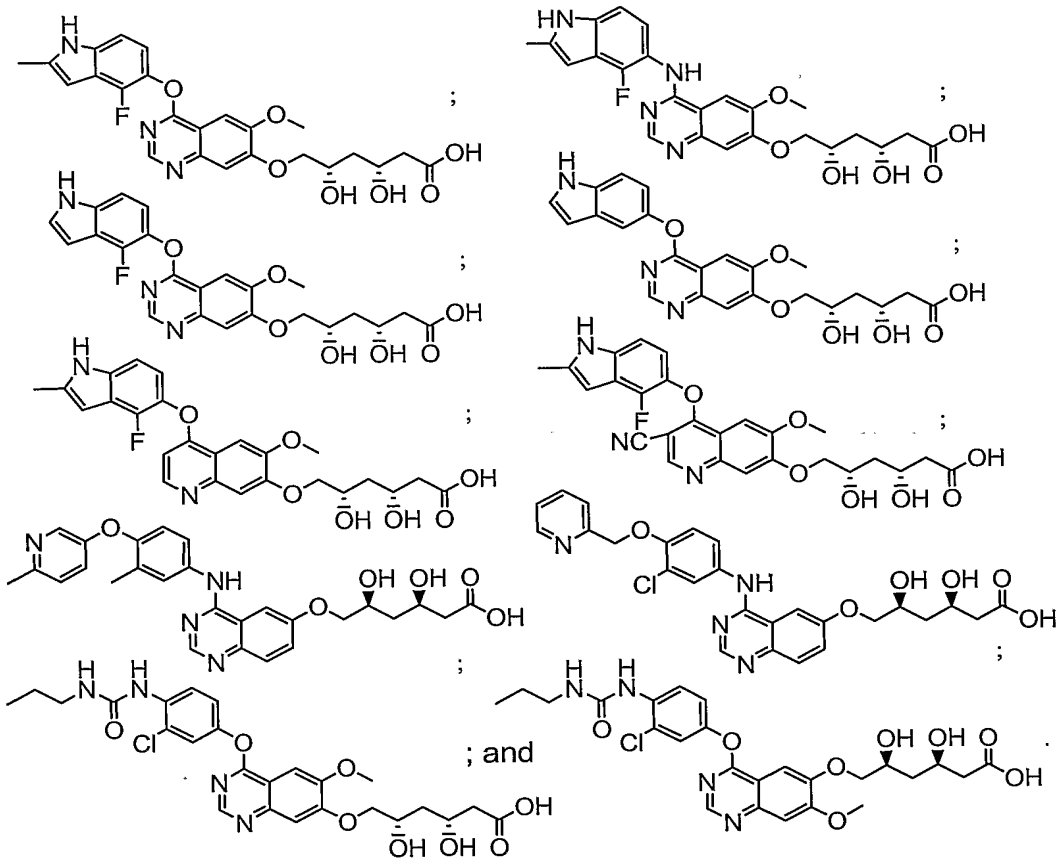
4. The compound or salt of claim 2, wherein the compound is selected from the group represented by the following structures:



; and

.

5. The compound or salt of claim 2, wherein the comp ound is selected from the group represented by the following structures:

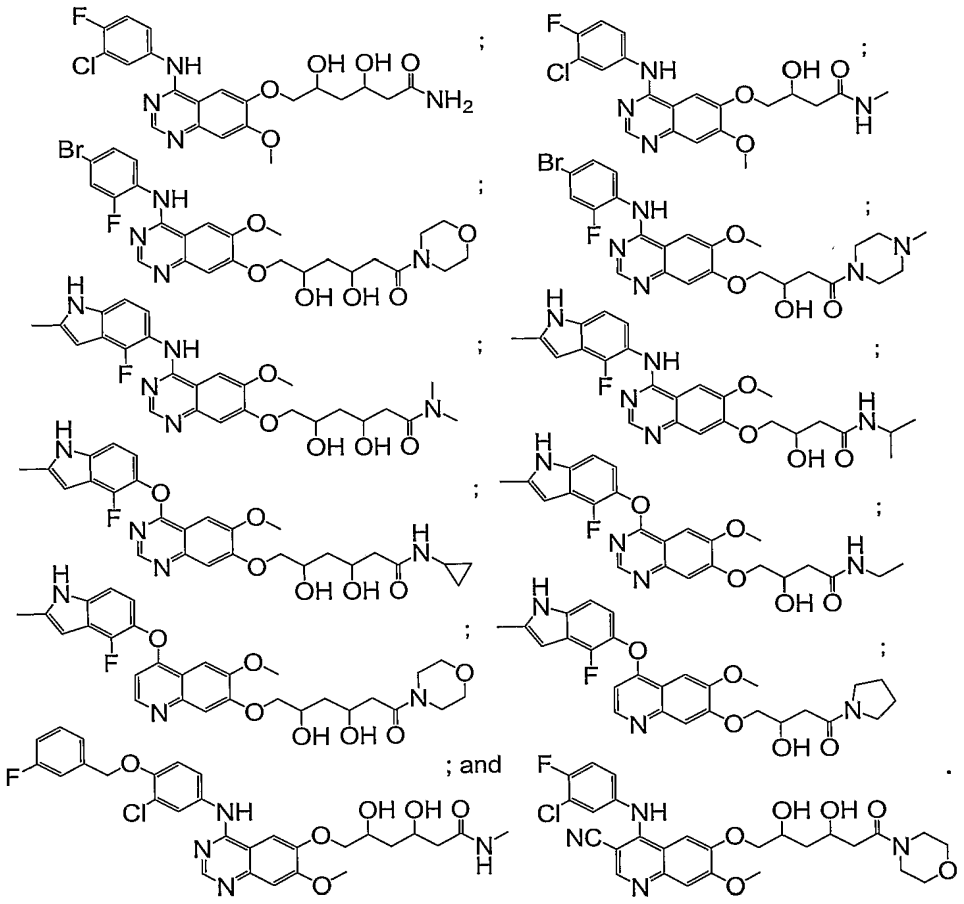


; and

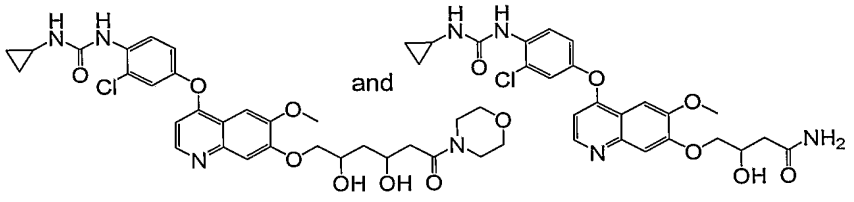
.

6. The compound, salt, tautomer, or prodrug according to claim 1 wherein R^2 is $-NR^5R^6$.

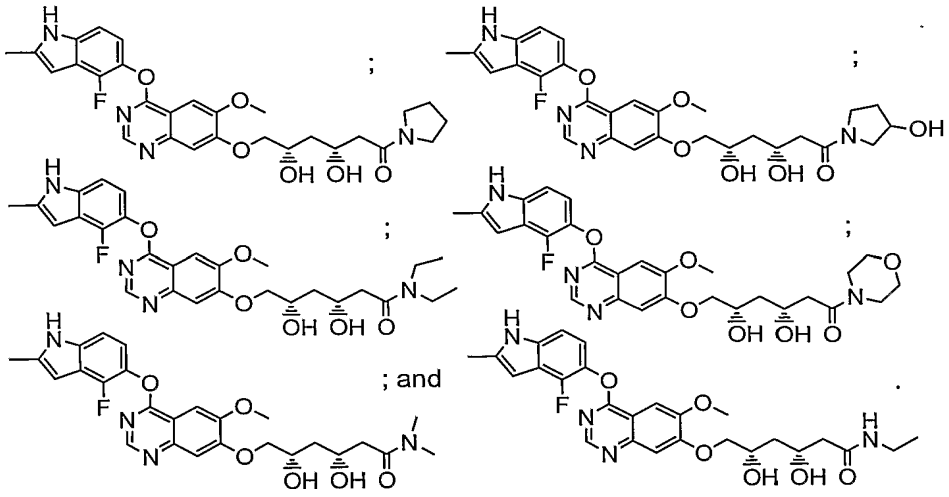
7. The compound or salt of claim 6, wherein the compound is selected from the group represented by the following structures:



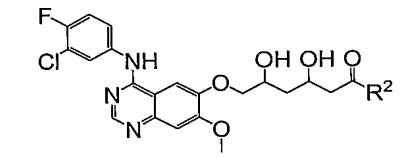
8. The compound or salt of claim 6, wherein the compound is selected from the group represented by the following structures:



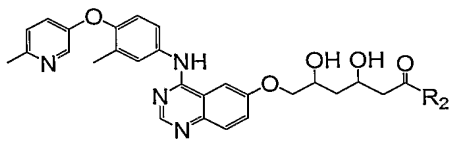
9. The compound or salt of claim 6, wherein the compound is selected from the group represented by the following structures:



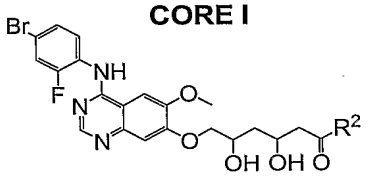
10. The compound or salt of claim 6, wherein the compound is selected from the group represented by the following structures:



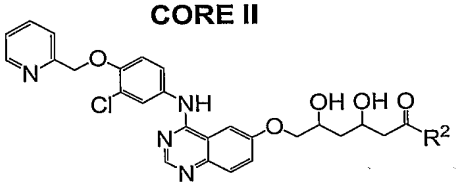
CORE I



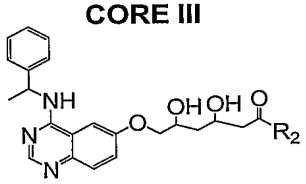
CORE II



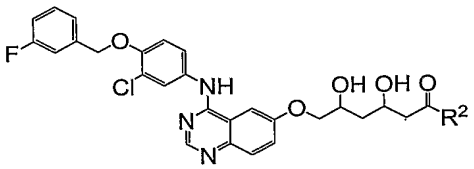
CORE III



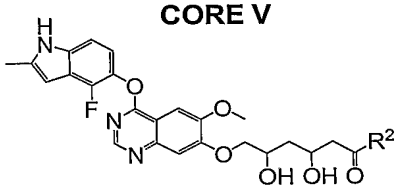
CORE IV



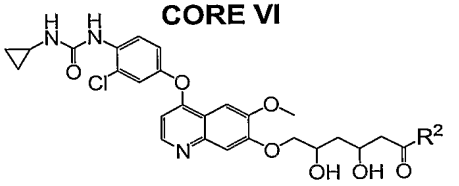
CORE V



CORE VI

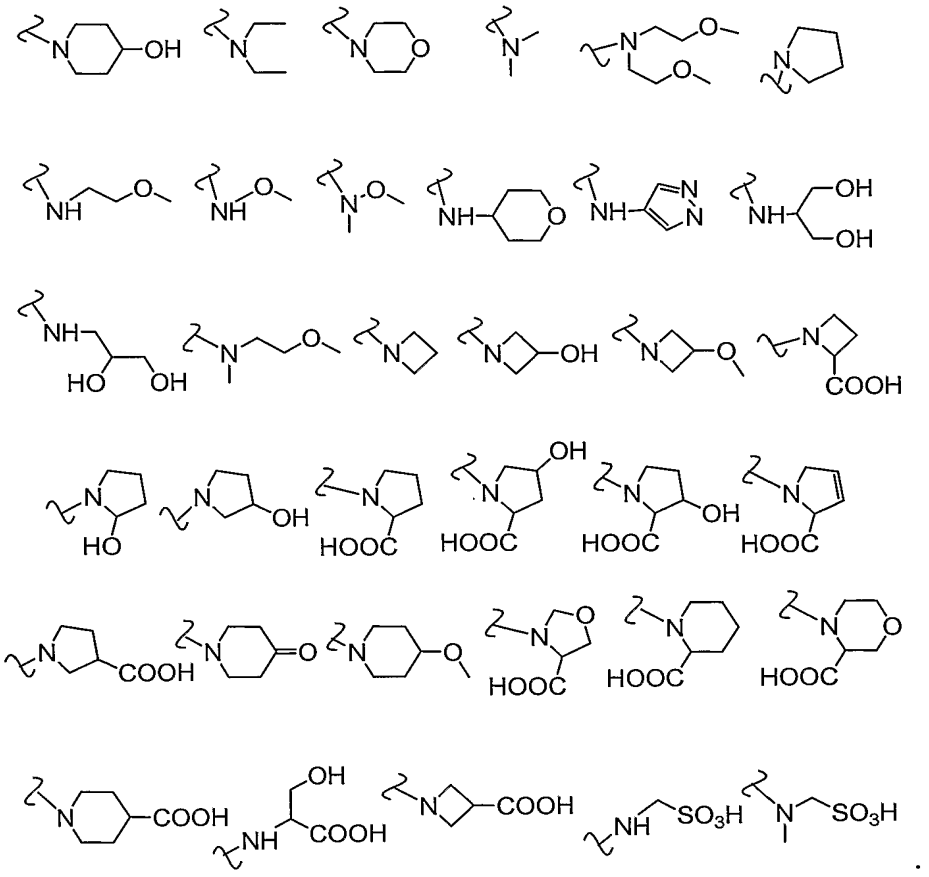


CORE VII

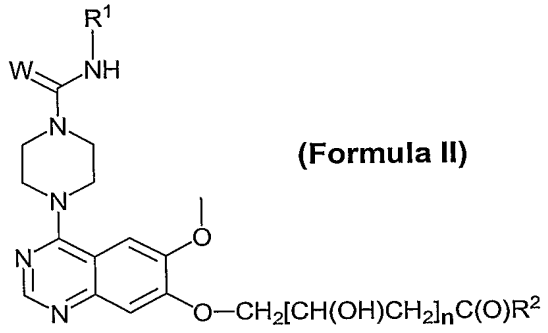


CORE VIII

wherein: R^2 is selected from the group consisting of radical represented by the following structures:



11. A compound of formula (**II**):



(Formula II)

wherein:

W is a diradical selected from the group consisting of O and S;

R^1 is a radical selected from the group consisting of optionally substituted phenyl, benzyl, heteroaryl, and heteroarylalkyl;

R^2 is a radical selected from the group consisting of hydroxyl, (C1-C6) alkoxy, (C3-C8) cycloalkoxy, and NR^3R^4;

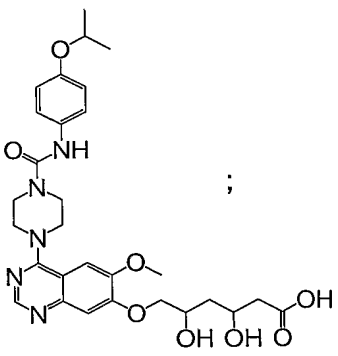
n is 1 or 2;

R^3 and R^4 are independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C1-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C1-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphoric acid, (C1-C6) alkyl sulfonic acid, (C1-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C10) aryl, (C5-C9) heteroaryl, (C3-C8) cycloalkyl carboxylic acid; or R^3 and R^4 together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids; or NR^3R^4 may form a cyclic ring containing 0-3 additional heteroatoms selected from N, O, or S;

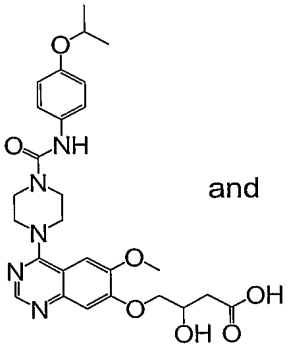
or, a pharmaceutically acceptable salt, its tautomer, a pharmaceutically acceptable salt of its tautomer, or a prodrug thereof.

12. The compound, salt, tautomer, or prodrug according to claim 11 wherein R^2 is a radical selected from the group consisting of hydroxyl, (C1-C6) alkoxy, and (C5-C8) cycloalkoxy.

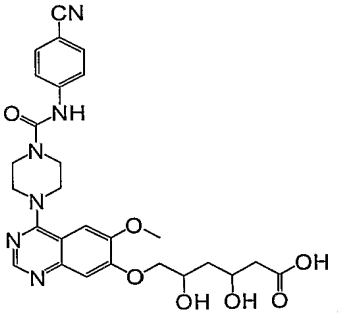
13. The compound or salt of claim 12, wherein the compound is selected from the group represented by the following structures:



;



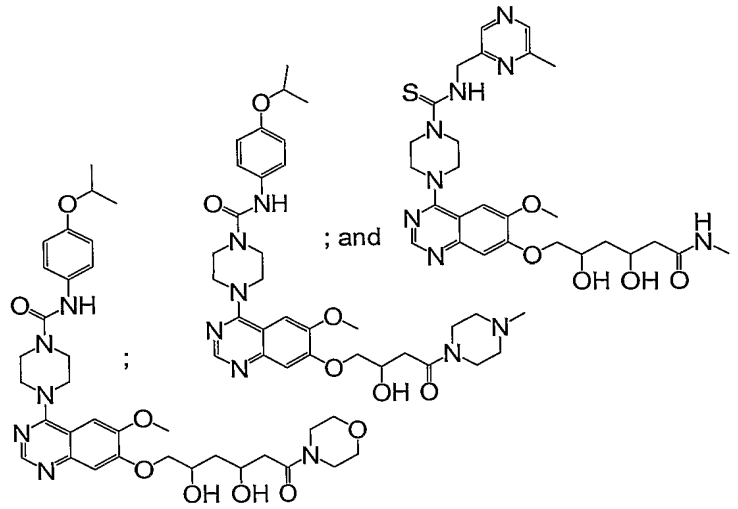
and



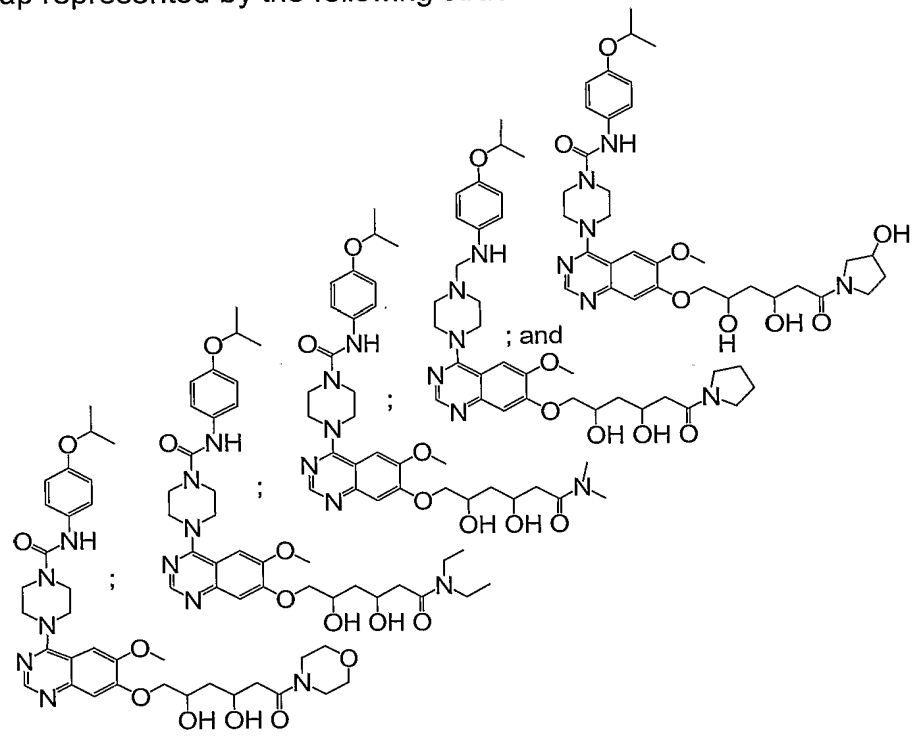
.

14. The compound, salt, tautomer, or prodrug according to claim 12 wherein R^2 is $-NR^5R^6$.

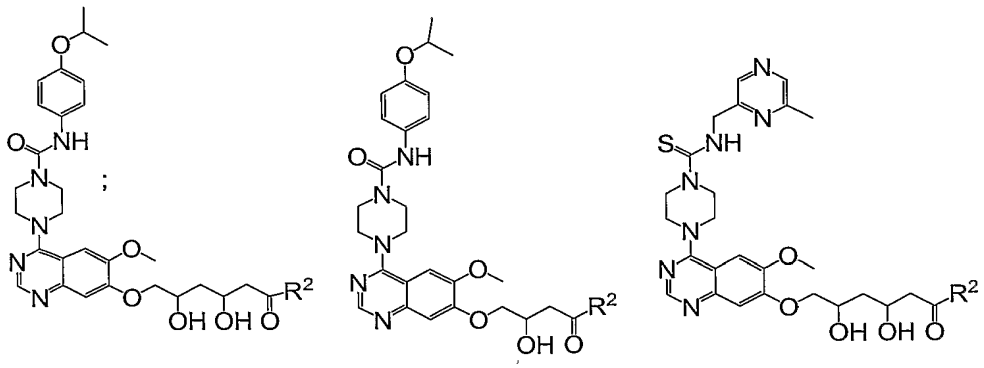
15. The compound or salt of claim 14, wherein the compound is selected from the group represented by the following structures:



16. The compound or salt of claim 14, wherein the compound is selected from the group represented by the following structures:

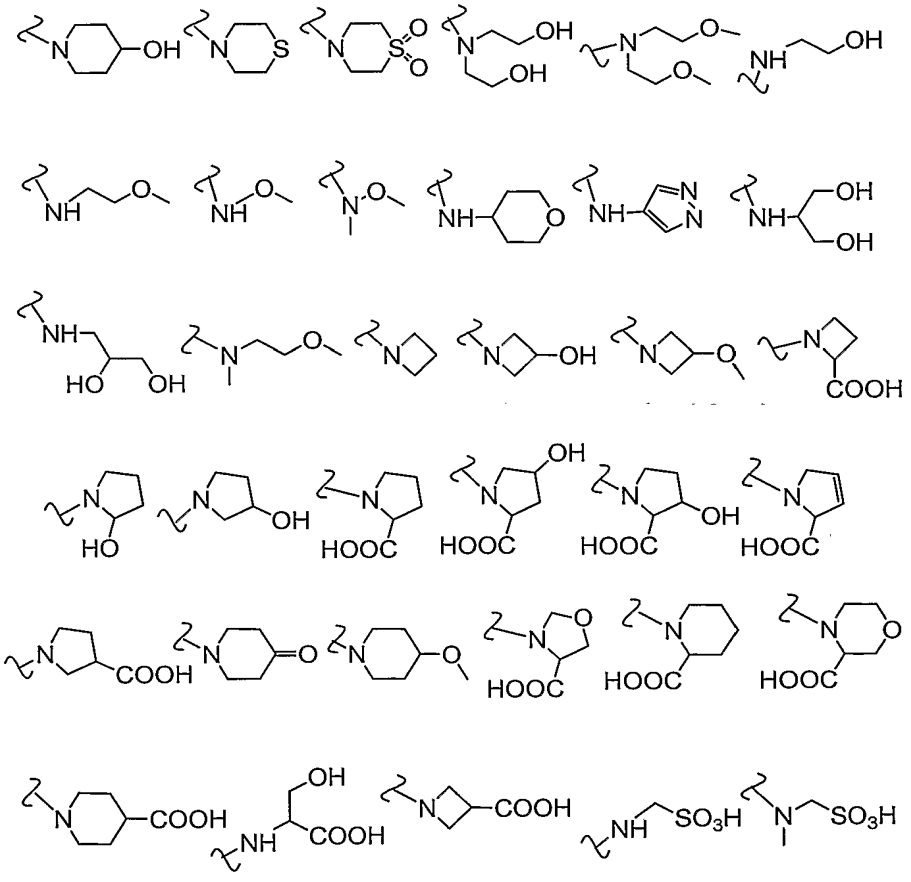


17. The compound or salt of claim 11, wherein the compound is selected from the group represented by the following structures:



CORE I CORE II CORE III

wherein: R^2 is selected from the group consisting of radical represented by the following structures:



18. The compound, salt, tautomer, or prodrug according to any of claims 1-10 with the following provisos:

the compound, salt, tautomer, or prodrug of claim 2 is excluded or

the compound, salt, tautomer, or prodrug of claim 3 is excluded or
the compound, salt, tautomer, or prodrug of claim 4 is excluded or
the compound, salt, tautomer, or prodrug of claim 5 is excluded or
the compound, salt, tautomer, or prodrug of claim 6 is excluded or
the compound, salt, tautomer, or prodrug of claim 7 is excluded or
the compound, salt, tautomer, or prodrug of claim 8 is excluded or
the compound, salt, tautomer, or prodrug of claim 9 is excluded or
the compound, salt, tautomer, or prodrug of claim 10 is excluded.

19. The compound, salt, tautomer, or prodrug according to any of claims 11-17 with the following provisos:

the compound, salt, tautomer, or prodrug of claim 12 is excluded or
the compound, salt, tautomer, or prodrug of claim 13 is excluded or
the compound, salt, tautomer, or prodrug of claim 14 is excluded or
the compound, salt, tautomer, or prodrug of claim 15 is excluded or
the compound, salt, tautomer, or prodrug of claim 16 is excluded or
the compound, salt, tautomer, or prodrug of claim 17 is excluded.

20. A method for the modulation of the catalytic activity of a protein kinase with a compound or salt of any one of claims 1-19.

21. The method of claim 20, wherein said protein kinase is selected from the group consisting of VEGF receptors, FGF receptors, EGF receptors, PDGF receptors.

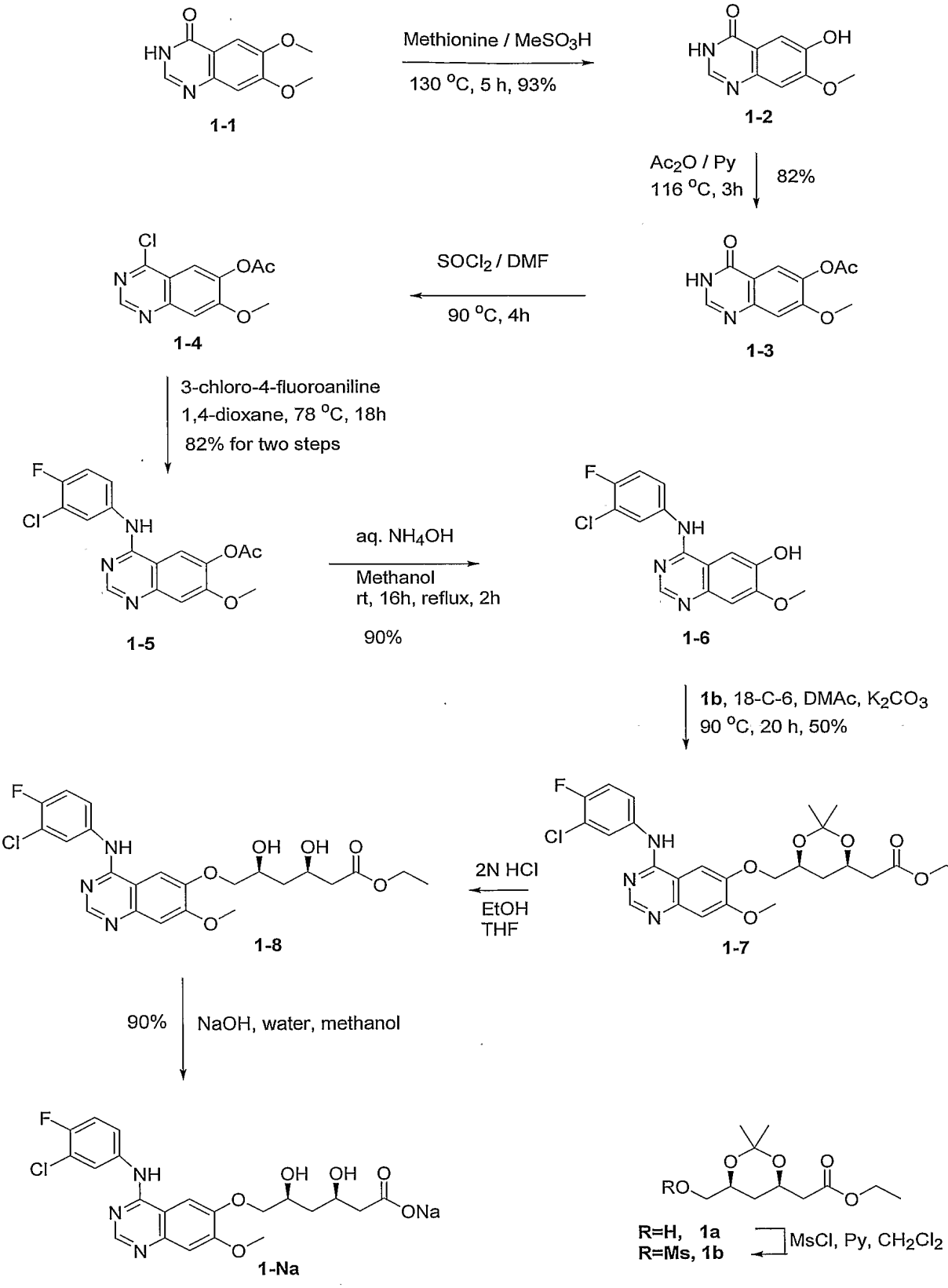

Methionine / MeSO3H
130 °C, 5 h, 93%
1-1
1-2
Ac2O / Py
116 °C, 3h
82%
SOCl2 / DMF
90 °C, 4h
1-4
1-3
3-chloro-4-fluoroaniline
1,4-dioxane, 78 °C, 18h
82% for two steps
aq. NH4OH
Methanol
rt, 16h, reflux, 2h
90%
1-5
1-6
1b, 18-C-6, DMAc, K2CO3
90 °C, 20 h, 50%
2N HCl
EtOH
THF
1-8
1-7
90%
NaOH, water, methanol
1-Na
R=H, 1a
R=Ms, 1b
MsCl, Py, CH2Cl2

Figure 1

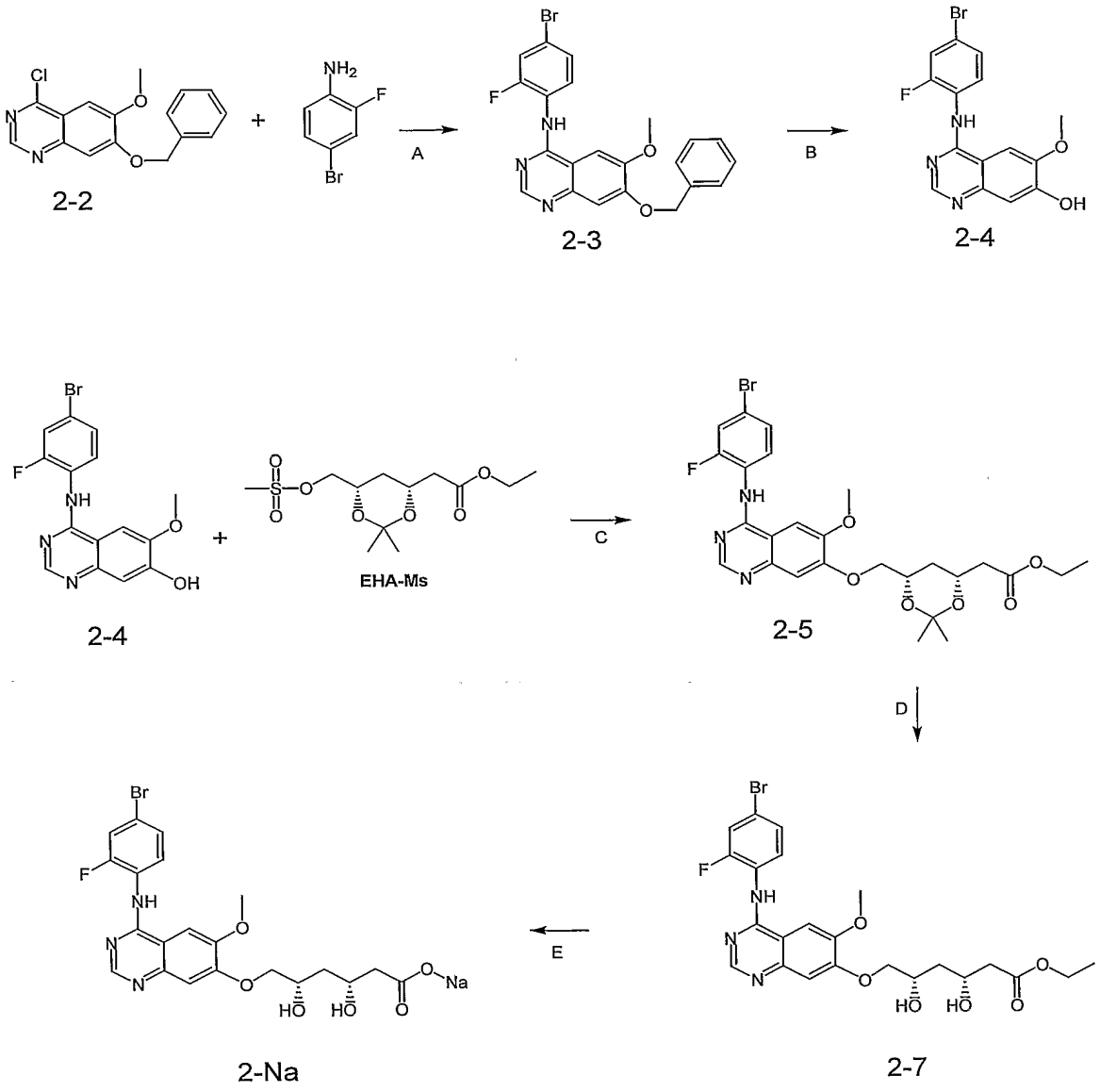


Figure 2

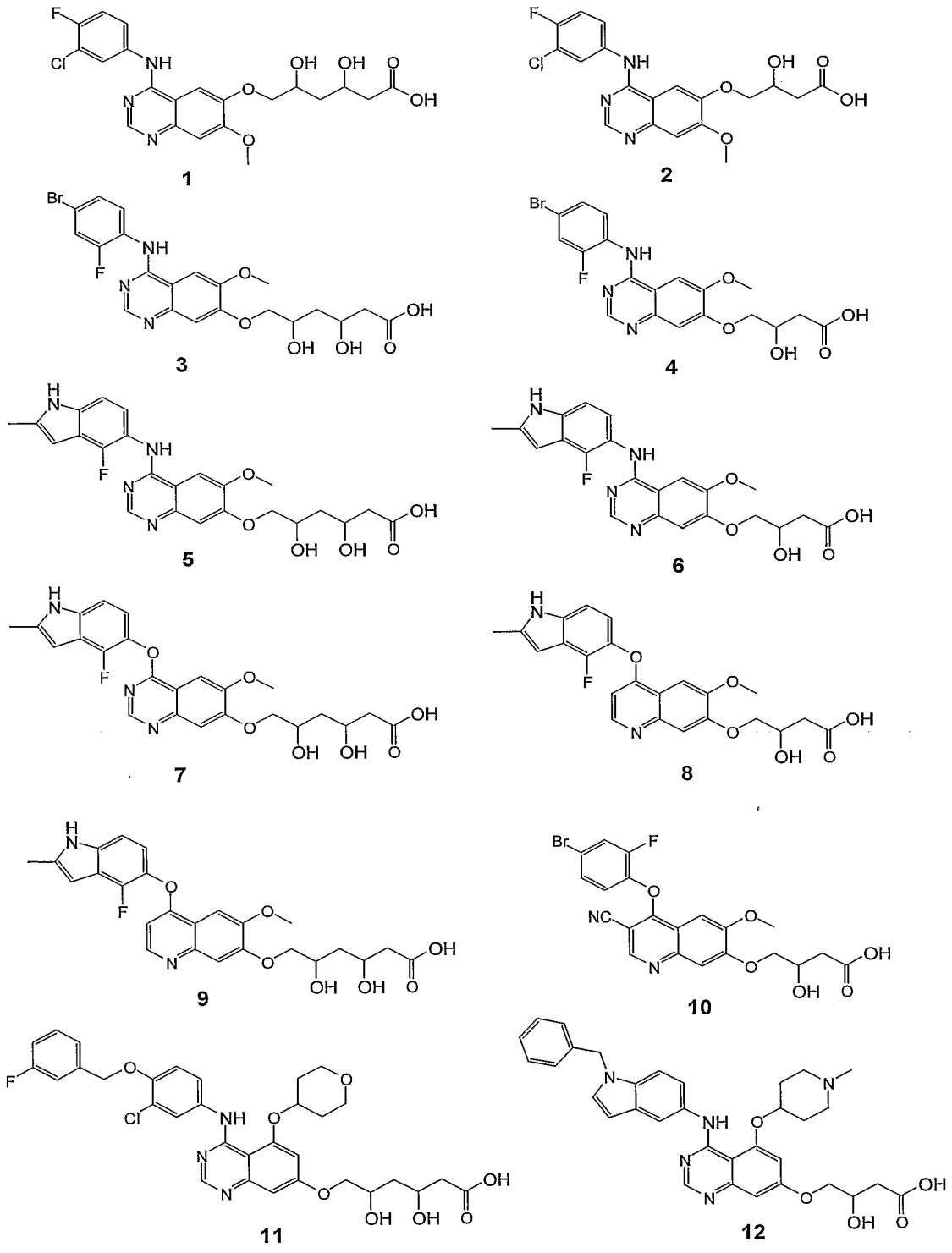


Figure 3A

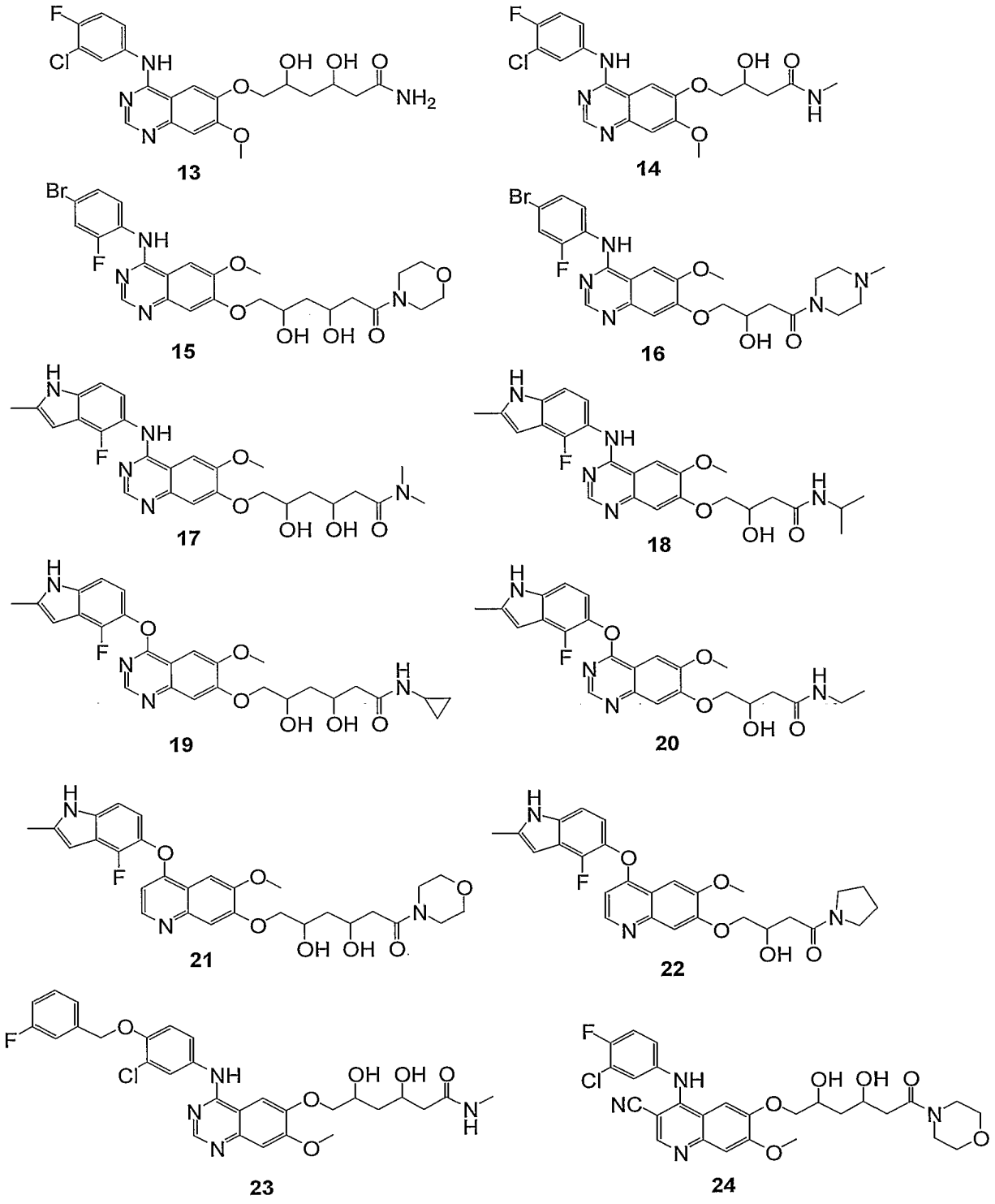
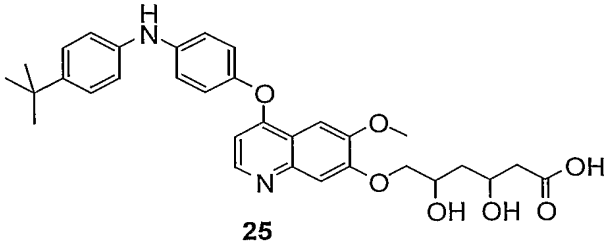
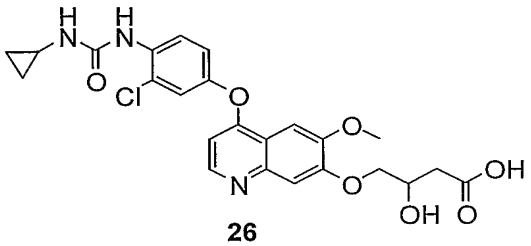


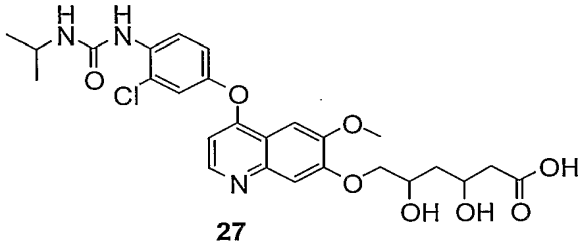
Figure 3B



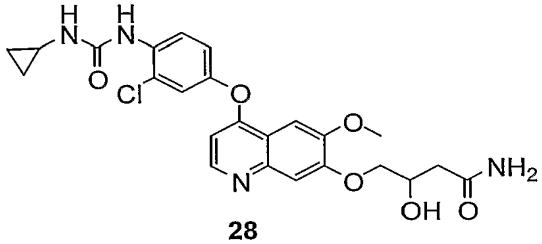
25



26



27



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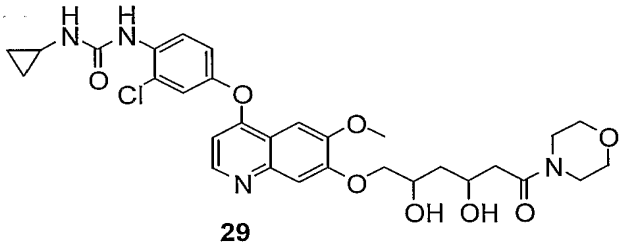
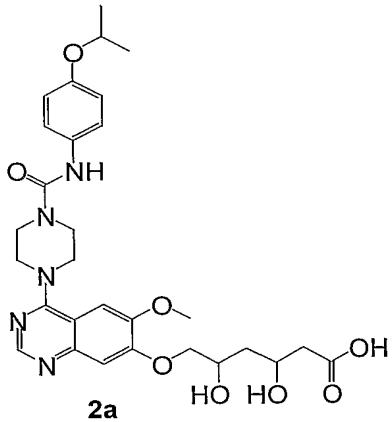


29

Figure 3C



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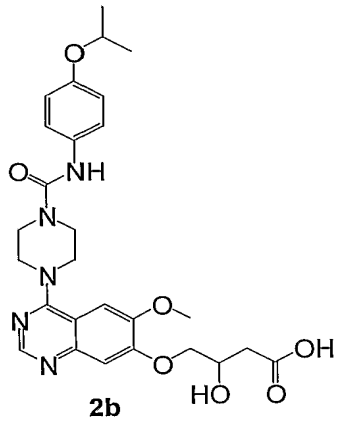
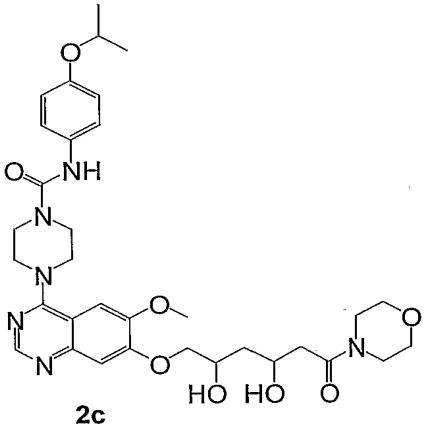


2b



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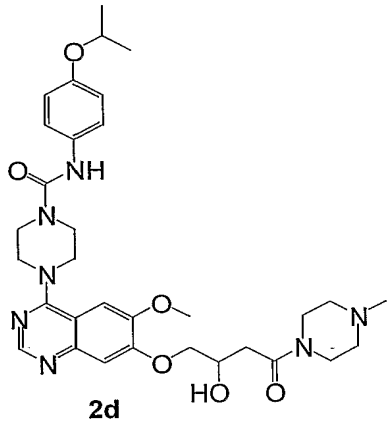
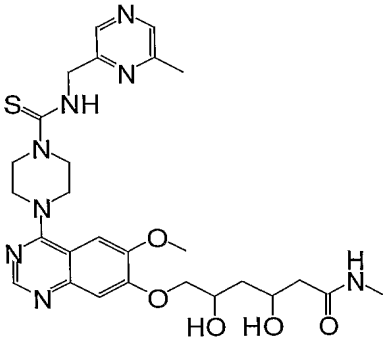
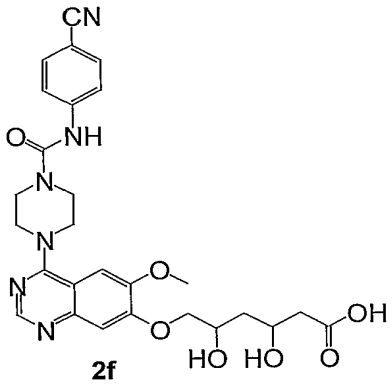


2d



2e



2f

Figure 4